ALTERNATING CURRENT POLAROGRAPHY OF ORGANIC COMPOUNDS

I. GENERAL INTRODUCTION AND THEORY

By B. BREYER,* H. H. BAUER,* and S. HACOBIAN*

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Summary

The theoretical principles governing the alternating current polarography of organic compounds are presented. The role of adsorption, and the relationship between the A.C. and D.C. criteria of polarographic reversibility are discussed.

I. INTRODUCTION

In a previous communication (Breyer 1953), the results obtained in these Laboratories over the past few years, while extending the applications of the A.C. polarographic method to the field of reducible organic compounds, have been briefly described and discussed. It was shown that these results differ in a marked way from those observed in the study of inorganic ions (Breyer, Gutmann, and Hacobian 1950, 1951; Breyer and Hacobian 1951*a*, 1951*b*) and also from those observed with surface-active, non-reducible substances. The latter produce a type of wave which has been called a "tensammetric wave" (Breyer and Hacobian 1952) to distinguish it from the ordinary polarographic wave which is due to a reduction process occurring at the electrode.

It is the purpose of the present paper to give a more detailed account of the principles underlying the alternating current polarography of reducible organic compounds.

II. TYPICAL EXPERIMENTAL RESULTS

The experimental results described here refer to aqueous, buffered solutions of the compounds examined. A sinusoidal voltage of 15 mV r.m.s. and 50 c/s was superimposed on the D.C. voltage.

(*a*) *Summit Potential and Half-Step Potential*

The potential corresponding to the peak of the A.C. wave of reducible organic compounds—the summit potential E_s—coincides generally with the half-step potential of the D.C. polarogram within ± 50 mV.

(*b*) *A.C. Waves and Shape of D.C. Polarograms*

With inorganic ions, A.C. waves are produced only in cases where the log $(i_d - i)/i$ *v.* E plot of the D.C. step is linear and of theoretical slope. Such plots are the exception with organic compounds, the majority of which nevertheless produce A.C. waves corresponding to the D.C. reduction wave.

* Physico-Chemical Laboratories, Faculty of Agriculture, University of Sydney.

(c) *Adsorption*

Organic compounds are usually adsorbed at the mercury-solution interface. This is demonstrated by a lowering of the base current of the supporting electrolyte (Breyer and Hacobian 1952), observed either at more positive potentials than the reduction wave, or at more negative potentials, or on both sides of the wave, according to whether adsorption occurs in the oxidized form, the reduced form, or both.

In many cases, tensammetric waves have been observed in addition to the polarographic A.C. waves.

(d) *Alternating Current and Bulk Concentration*

In general, the D.C. and A.C. calibration curves (current *v.* bulk concentration) of inorganic ions are linear. With organic compounds, only the D.C. curves are linear, whereas the A.C. plots show a marked non-linearity, that is, the currents tend to a limiting value at higher bulk concentrations (most commonly between 10^{-4} and 10^{-3}M).

Many organic compounds show A.C. waves at much lower bulk concentrations than do inorganic ions. Thus, for instance, whilst Cd^{++} ions do not show an A.C. wave at bulk concentrations lower than 10^{-5}M, chloranilic acid gives a wave at a concentration of 10^{-7}M, and methylene blue at 10^{-6}M, to quote but two examples.

(e) *Alternating Current and Height of Mercury Reservoir*, H

Whereas the D.C. diffusion current varies as $H^{\frac{1}{2}}$, the alternating current is independent of H.

(f) *Effect of Surface-Active Substances*

The A.C. waves due to inorganic ions are very sensitive to the presence of surface-active substances (Breyer and Hacobian 1952), whereas the waves due to the reduction of organic compounds are often much less affected. Thus the A.C. wave of Cd^{++} ions disappears completely in the presence of M/10 *cyclo*-hexanol, while under the same conditions the A.C. wave of *m*-nitrophenol is lowered by only about 10 per cent.

The presence of reducible organic compounds also affects the tensammetric waves produced by surface-active substances; for instance, the presence of increasing amounts of *m*-nitrophenol first raises, then lowers, the height of the negative tensammetric wave of octanol, and progressively shifts the summit potential from $-1{\cdot}2$ to $-1{\cdot}4$ V *v.* saturated calomel electrode (S.C.E.) (Fig. 1).

Full details of these investigations will be published in subsequent papers of this series.

III. Discussion

(a) *D.C. Process and A.C. Waves*

An A.C. wave is produced when the relevant part of a particular electrode process proceeds reversibly. However, the log $(i_d-i)/i$ *v.* E plot of the D.C. step is not an unambiguous criterion for determining whether or not a reduction is proceeding reversibly.

A polarographically reversible process is defined as one which follows the Heyrovsky-Ilkovič equation

$$E = E_{\frac{1}{2}} + \frac{RT}{nF} \ln \frac{i_d - i}{i}. \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

In such a process, it can be inferred that the electron transfer reaction is reversible, that is, it follows the Nernst equation

$$E = E_0 + \frac{RT}{nF} \ln \frac{a_{Ox}}{a_{Red}}, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

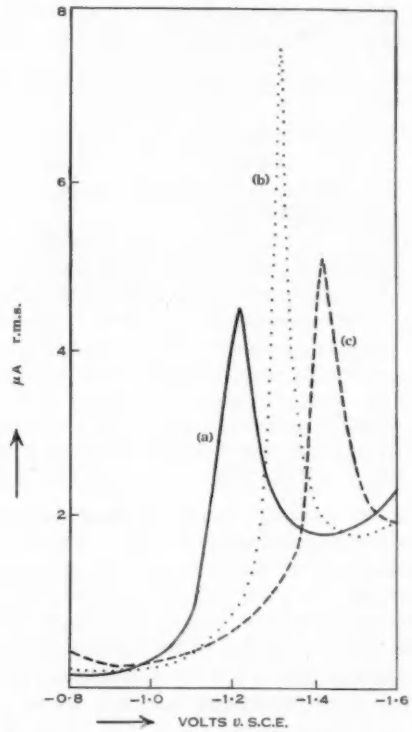

Fig. 1.—(*a*) Tensammetric wave of octanol (saturated solution) in Prideaux and Ward buffer, pH 4 ; (*b*) same after addition of 5×10^{-4}M nitrophenol ; (*c*) same after addition of 2×10^{-4}M nitrophenol.

and that the polarographic conditions of current flow through the electrode have no measurable disturbing influence on the equilibrium conditions subsisting at the electrode. Hence in a polarographically reversible process, the electrode reaction proceeds reversibly, and an A.C. wave is produced.

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A reduction process may not follow equation (**1**) for two reasons :

(i) the electrode reaction is not proceeding reversibly, and no A.C. wave is produced, or

(ii) part of the electrode reaction proceeds reversibly and an A.C. wave is produced despite a non-theoretical log plot.

Case (i).—The electrode process can occur irreversibly because :

(1) The electron transfer reaction is thermodynamically irreversible.

(2) The rate of the electron transfer reaction is slow compared with the rate of some other reaction preceding or succeeding it.

(3) The rate of diffusion of the electroactive forms to and from the electrode is fast compared with the rate of the electrode process (cf. Delahay 1953).

Case (ii).—Despite a non-theoretical log-plot, some part of the electrode process occurs reversibly. This is the case when :

(1) More or less stable intermediates are formed. Even when all the separate steps in the reduction occur reversibly, the log plot corresponding to the whole reduction process may be non-linear (cf. reduction via semiquinones, Müller 1940).

(2) The reduction involves several electron transfer steps, some of them reversible, others irreversible. Here the shape of the D.C. polarogram is non-theoretical, but parts of the process are reversible.

(3) One or both of the electroactive forms are adsorbed at the electrode and as a consequence two D.C. steps appear. One of these steps is often polarographically reversible and yields the theoretically required log plot (Brdička 1947). There will be cases, however, where the steps are so close together on the potential scale that they cannot be distinguished ; here the log plot, calculated for the whole process, is non-theoretical, despite the fact that part of the reduction proceeds reversibly.

In the reduction of inorganic ions, polarographic irreversibility is almost invariably due to factors discussed under case (i) ; in other words, the electrode process is in fact proceeding irreversibly, and no A.C. wave is produced. On the other hand, polarographic irreversibility in the reduction of organic compounds may be due to processes mentioned under case (ii), that is, there may be a reversible step in the overall process, and hence an A.C. wave is produced.

Thus, especially in the case of organic compounds, the log plot is not an unambiguous criterion of the production of an A.C. wave.

(*b*) *The Organic A.C. Polarographic Wave*

Figure 2 represents schematically the electrode-solution system (cf. Breyer and Hacobian 1954).

Region IV is the bulk of the solution, unaffected by conditions at the electrode ; region III is the space in which diffusion occurs under the influence of the concentration gradient existing between regions IV and II. Regions I and II together form the " potential-determining " region ; region I (corresponding to the rigid double layer) having a thickness of the same order as the

dimensions of a single molecule or ion, while region II corresponds to the space within which the electrode reaction occurs. As stated previously (Breyer and Hacobian 1954), the concentrations of the electroactive forms in regions I and II are independent of distance from the electrode, in the sense that the diffusion of ions giving rise to the D.C. polarographic current occurs only in region III.

It has been mentioned that organic compounds are typically adsorbed at the mercury-solution interface; in other words, the concentration of, say, oxidized form in region I, $C_{Ox\,I}$, is not equal to that in region II, $C_{Ox\,II}$. This is essentially different to the case of inorganic ions, where $C_{Ox\,I}$ and $C_{Ox\,II}$ are equal.

It has been stated that the height of the A.C. wave is independent of the height of the mercury reservoir; this means that the alternating current is directly proportional to the surface area of the dropping electrode. It follows that the alternating current is determined by the *surface concentration* of electroactive forms in region I, in contradistinction to the D.C. diffusion current which depends on the *concentration gradient* between region IV and region II.

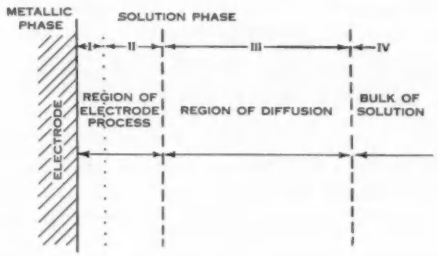

Fig. 2.—Schematic representation of the electrode-solution system in the absence of an A.C. field.

(i) *Correspondence of Summit Potential* E_s *and Half-Step Potential* $E_{\frac{1}{2}}$.—The summit potential of the A.C. wave occurs at that potential where the concentration change due to the periodic oxidation-reduction process is of maximum amplitude, that is, when the concentrations of the oxidized and the reduced form in region I are equal. On the other hand, the half-step potential corresponds to that potential at which the D.C. current is half of its maximum value, and thus depends on the concentrations of the electroactive forms in region II, and not, as does E_s, on the concentrations in region I.

It is apparent that E_s and $E_{\frac{1}{2}}$ will coincide exactly only then, when neither of the forms is adsorbed and the reduction is polarographically reversible. As already mentioned, an exact correspondence of E_s and $E_{\frac{1}{2}}$ has not been observed in general with organic compounds.

(ii) *Height of the Wave.*—The height of an A.C. wave depends on the amplitude of the periodic concentration change set up in region I by the superposed alternating voltage (Breyer and Hacobian 1954). Thus

$$i_{\sim(E_s)} = y\Delta C_{I(E_s)}, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

where $i_{\sim(E_s)}$ is the alternating current at the summit potential,
$\Delta C_{I(E_s)}$ is the amplitude of the corresponding concentration change in region I, and
y is a proportionality constant.

Further

$$\Delta C_{I(E_s)} = \beta_{(E_s)} C_{I(E_s)}, \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

where $C_{I(E_s)}$ is the concentration (of either oxidized or reduced form) in region I at E_s and $\beta_{(E_s)}$ depends on the geometry of the D.C. step about E_s, on the thermodynamic reversibility of the electron transfer reaction, and on the frequency and amplitude of the alternating voltage.

Now, the concentration in region I is an adsorption function of the concentration in region II, so that

$$C_{I(E_s)} = f(s, C_{II(E_s)}), \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

where f denotes the adsorption function and s is the surface area of the drop. For the D.C. polarographic current, provided the shape of the step does not change with concentration,

$$i_{(E)} = k(C_B - C_{II(E)}), \quad \ldots\ldots\ldots\ldots\ldots\ldots (6)$$

where k is a constant for a particular substance and C_B is the bulk concentration.

Since the D.C. calibration curve is typically linear

$$i_{(E)} = k'_{(E)} C_B, \quad \ldots\ldots\ldots\ldots\ldots\ldots (7)$$

where $k'_{(E)}$ varies with the potential.

Combining equations (6) and (7)

$$C_{II(E)} = K_{(E)} C_B, \quad \ldots\ldots\ldots\ldots\ldots\ldots (8)$$

where $K_{(E)}$ varies with the potential, and depends on the particular substance.

Combining equations (3), (4), (5), and (8)

$$i_{\sim(E_s)} = y\beta_{(E_s)} f(s, K_{(E_s)} C_B). \quad \ldots\ldots\ldots\ldots\ldots (9)$$

The adsorption function f in general will not be a simple one, since it depends on the adsorption coefficients of the oxidized form, of the reduced form, and of possible intermediates, as well as on their concentrations at the interface. In many cases, it has been possible to fit a function of the type of the Langmuir isotherm to the A.C. calibration curves observed; in others, modifications of this function are necessary. Details will be given in subsequent papers of this series.

(iii) *Nature of the Wave.*—A.C. waves are produced either by a reversible reduction process, or by an adsorption-desorption process. The mechanism of current flow in the two cases is quite different. It will be shown in the following that the mechanism of the A.C. process in the reduction of organic compounds differs from that of a "normal" (inorganic) reduction process, and from that of a tensammetric process.

(1) *Reversible Inorganic Reduction Processes.* In that range of applied D.C. potential where the oxidation-reduction process occurs, the superposed alternating voltage gives rise to a periodic change in concentrations of oxidized and reduced forms. Alternating current flows as a *direct* result of this concentra-

tion change, and in fact the magnitude of the current can be predicted accurately from an equation derived on the basis of such a mechanism (Breyer and Hacobian 1954).

(2) *Adsorption-Desorption Processes.* It is a well-known fact that surface-active substances, spontaneously adsorbed at the mercury-solution interface, are desorbed when the potential across the interface is greater than a certain critical value. Around this value (which depends on the nature of the substance, its concentration, on the supporting electrolyte, temperature, and so on) a superposed alternating voltage gives rise to a periodic adsorption-desorption process and an A.C. wave is produced. The alternating current which flows in this case—"*tensammetric current*"—is due to a periodic movement of "active charges" (Breyer and Hacobian 1952) in the vicinity of the interface; at the same time, the electrode is polarized with respect to D.C.

(3) *Organic Reduction Processes.* As in the case of inorganic reductions, a periodic change in concentrations of oxidized and reduced forms at the electrode is set up. Alternating current flows as a direct result of this change. However, at the same time the organic substance behaves as an active charge at the interface; further, the nature of this active charge depends on whether the substance is in the oxidized or the reduced form. Thus the transformation of oxidized and reduced forms by virtue of electron transfer gives rise to a transformation and movement of active charges in the vicinity of the electrode. This transformation and movement of active charges, which accompanies electron transfer in the case of organic compounds, gives rise to an additional tensammetric current over and above that which flows as a *direct* result of the periodic electron transfer reaction. These combined currents have been termed "rearrangement current" (Breyer 1953).

(iv) *Sensitivity.*—It has been mentioned that the A.C. polarographic method is often more sensitive to organic compounds than to inorganic ions. The reasons for this are now clear. For a given bulk concentration, the interfacial concentration of organic substance will be greater as a result of adsorption. Further, for a given interfacial concentration, the resulting current in the case of an organic compound will be greater than for an inorganic ion by virtue of the additional tensammetric current flowing as a result of the "rearrangement" of the organic substance at the interface.

In subsequent papers of this series, it will be shown how the principles discussed here apply to the different classes of organic compounds.

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DIRECT CURRENT POLAROGRAPHY IN THE PRESENCE OF ALTERNATING VOLTAGES

II. IRREVERSIBLE SYSTEMS

By G. S. BUCHANAN* and R. L. WERNER*

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Summary

The superposition of a small alternating voltage on the normal D.C. voltage applied at the dropping mercury electrode (D.M.E.) results in the case of irreversible systems in a marked displacement of the entire D.C. wave, in contradistinction to those cases known to be reversible. Such a displacement has been interpreted in terms of an ionic picture.

The cases examined were ZnO_2^{--}, Fe^{++}, Ni^{++}, Sb^{+++} in the presence of varying concentrations of Cl^-, and Cd^{++} in the presence of varying concentrations of *cyclo*hexanol. The effect of frequency was investigated.

I. INTRODUCTION

In Part I of this series (Buchanan and Werner 1954) the effect of an applied alternating voltage on the current voltage curves obtained in the usual manner at the dropping mercury electrode (D.M.E.) was discussed with reference to reversible systems. In the present paper the methods described in the earlier paper (loc. cit.) have been extended to some irreversible systems using the apparatus and methods described previously.

II. RESULTS

In Figure 1 are shown three typical curves obtained in the case of three inorganic ions which are known to be irreversibly reduced at the D.M.E.

In each of the three cases, namely, $1{\cdot}0\times10^{-3}$M Ni^{++} in $1{\cdot}0\times10^{-1}$M KCl, $1{\cdot}0\times10^{-3}$M Fe^{++} in $1{\cdot}0\times10^{-1}$M KCl, and $1{\cdot}0\times10^{-3}$M ZnO_2^{--} in $1{\cdot}0\times10^{-1}$M NaOH, the curves obtained are similar to each other and differ from the type obtained with reversible systems (Buchanan and Werner loc. cit.). It will be observed that the *Z* curve is completely displaced to more positive potentials with reference to the *Y* curve. This displacement depends on the magnitude of the alternating voltage applied and is shown in each case for 100 mV r.m.s. sine wave. The diffusion currents of the *Y* and *Z* curves, shown in Figure 1, are not quite equal. This appears to be due to the effect of the applied A.C. on the m and t of the drop. The magnitude of this effect in the case of the ZnO_2^{--} ion is shown in Table 1.

The effect of frequency is shown in Figure 2 for the case of Ni^{++} ion in $1{\cdot}0\times10^{-1}$M KCl.

* Department of Physical Chemistry, N.S.W. University of Technology, Broadway, Sydney.

The separation decreases with increasing frequency and has practically disappeared at 5000 c/s, owing presumably to the failure of the ions to follow the field at the higher frequencies. Other ions behave similarly.

In terms of the explanation for the reversible systems given in Part I of this series, the drop is always more negative in these irreversible cases than the

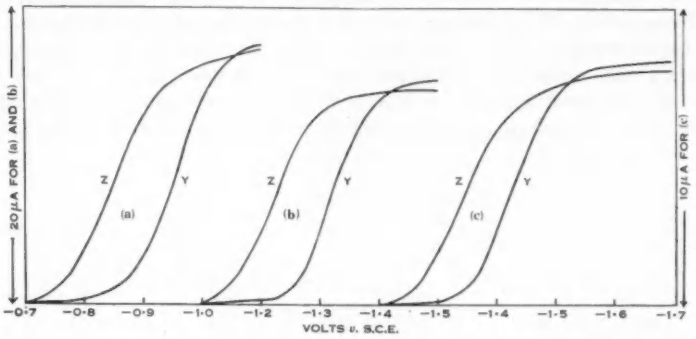

Fig. 1.—*Y* and *Z* curves for some irreversible cases. Curve (*a*) $1{\cdot}0\times10^{-3}$M Ni^{++} in $1{\cdot}0\times10^{-1}$M KCl+0·004 per cent. methyl orange; curve (*b*) $1{\cdot}0\times10^{-3}$M Fe^{++} in $1{\cdot}0\times10^{-1}$M KCl+0·004 per cent. gelatin; curve (*c*) $1{\cdot}0\times10^{-3}$M ZnO_2^{--} in $1{\cdot}0\times10^{-1}$M NaOH. A.C. = 100 mV r.m.s. 30 c/s sine wave. $T=25$ °C. For values of m and t see Table 1. The methyl orange and gelatin removed maximum in both the *Y* and *Z* curves but did not appear to affect the separation. The solutions were air-free.

D.C. set on the slidewire as a result of a rectification of the applied A.C. in one direction. Unlike the reversible case this applies throughout the entire curve, resulting in a displacement, without change in shape, to more positive potentials on the D.C. axis.

TABLE 1

VALUES OF m, t, AND $m^{2/3}t^{1/6}$ FOR $1{\cdot}0\times10^{-3}$M ZnO_2 IN $1{\cdot}0\times10^{-1}$M NaOH

$T=25$ °C

Values of:	Direct Current		Direct Current	
	1·6 V	1·6 V+100 mV A.C.	1·7 V	1·7 V+100 mV A.C.
m (mg sec^{-1}) ..	2·30	2·31	2·32	2·30
t (sec)	6·29	2·24	2·41	2·07
$m^{2/3}t^{1/6}$	2·05	2·00	2·03	1·97

The phenomena can be interpreted in terms of ionic movement in the following way. Consider the case of Ni^{++} ion and a point on the rising part of the curve. As the alternating voltage increases negatively, Ni^{++} ions are discharged at a greater rate than that due to the applied D.C., but are not

redissolved during the positive half-cycle, due to some barrier hindering the dissolution of the Ni atoms from the drop surface. As a result of this process a net current flows from the solution to the electrode in excess of that due to the applied D.C. potential alone, hence any point on the *Z* curve falls above the *Y* curve at a given D.C.

The explanation given above is supported by the potential-time curves of Heyrovsky (1947, Fig. 5) which indicate that the Ni^{++} ion is discharged as the drop becomes negative but is not redissolved as the potential decreases to zero, indicating the complete irreversibility of the reduction process in this case. However, the potential-time curves of Heyrovsky indicate that zinc atoms are, in fact, redissolved at more positive potentials (−0·87 V) than that at

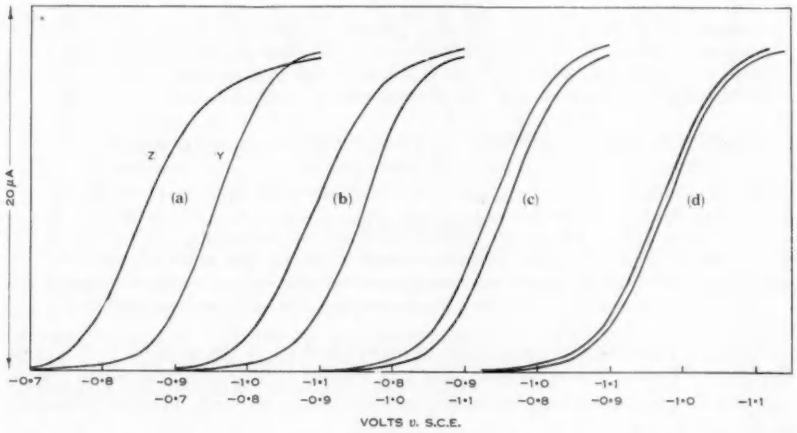

Fig. 2.—Effect of frequency on the separation of the *Y* and *Z* curves in the case of $1{\cdot}0\times10^{-3}$M Ni^{++} in $1{\cdot}0\times10^{-1}$M KCl+0·004 per cent. methyl orange. A.C.=100 mV r.m.s. T=25 °C. For m and t see Table 1. Curve (*a*) 30 c/s, curve (*b*) 1000 c/s, curve (*c*) 3000 c/s, curve (*d*) 5000 c/s. The solution was air-free.

which they are discharged (−1·46 V). This apparent degree of reversibility does not invalidate the above argument since the sweep voltages used here in the case of zinc (peak 141 mV) do not make the drop sufficiently positive to allow dissolution of the zinc atoms, at least, in that portion of the cathodic wave at which appreciable deposition is occurring (that is, at potentials more negative than *c.* −1·4 V).

The dissolution process may be more easily explored by an investigation of a zinc amalgam at the dropping electrode. Figure 3 shows the behaviour of an approximately 2×10^{-3}M zinc amalgam and a $1{\cdot}0\times10^{-1}$M NaOH solution (air-free).

It will be observed that the rectification process has been reversed and the direction of current flow is such that zinc is dissolved with the formation of zincate ion but is not redischarged on the negative sweep.

The complete behaviour of the system is shown in Figure 4 where both the anodic and cathodic curves are shown together.

The half-wave potentials of the normal anodic Y_a and cathodic Y_c waves are displaced, the anodic wave to the more positive potentials required for the dissolution process. The application of an alternating voltage in the range of D.C. voltages, required to cause dissolution of the zinc from an amalgam, will assist the dissolution process, since on the positive sweep zinc atoms will be dissolved more readily but will not be discharged on the negative sweep, for still more negative potentials are necessary for this process as shown by the Y_c curve.

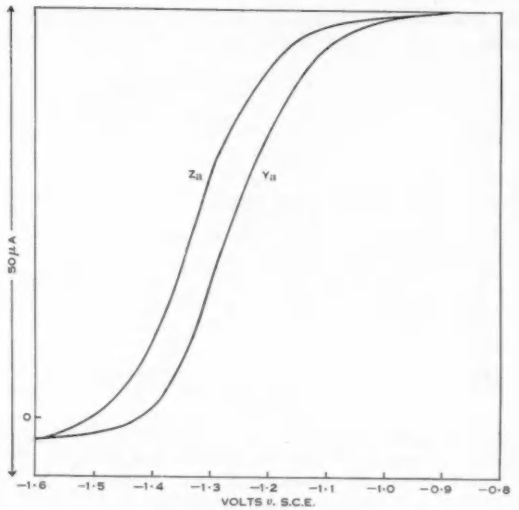

Fig. 3.—The effect of a superimposed A.C. on the D.C. polarogram of *c.* $2{\cdot}0\times10^{-3}$M zinc amalgam and 1·0M NaOH. A.C.=150 mV r.m.s. 30 c/s. T=25 °C. $m=2{\cdot}45$ mg sec^{-1}, $t=3{\cdot}38$ sec at D.C.=0·8 V and no A.C.; $m=2{\cdot}45$ mg sec^{-1}, $t=3{\cdot}32$ sec at D.C.=0·8 V and A.C.=150 mV. The solution was air-free.

It might be anticipated that the application of larger alternating voltages will cause the Y_c and Z_c curves and Y_a and Z_a curves to cross as in the reversible cases. Larger voltages were applied to the cathodic case and an indication of a cross-over point toward the top end of the step was obtained. Unfortunately, the results were not completely reliable due to the disturbance of the drop by the larger voltages.

It is interesting to follow cases in which successive steps change the system from reversibility to complete irreversibility. Breyer, Gutmann, and Hacobian (1951) report that the reversibility of Sb^{+++} discharge in $NaClO_4$.$HClO_4$ supporting electrolyte depends on the concentration of halide ions, as shown by

(i) variation in peak height of A.C. polarograms ; (ii) changing slope of log plot ; with change in halide ion concentration.

Similar solutions were examined by the method described. It was observed that a transition occurred from an irreversible to a reversible system. The process was marked by a displacement of the *Z* curve as well as a change in slope. The change may be followed by a movement of the cross-over point down toward the D.C. half-wave potential as the process becomes more reversible. The irreversibility in this case is essentially due to the failure of the antimony atoms to reform an ion in solution. The addition of the HCl assists the formation of an ion, probably a complex ion, and thus makes the process more reversible.

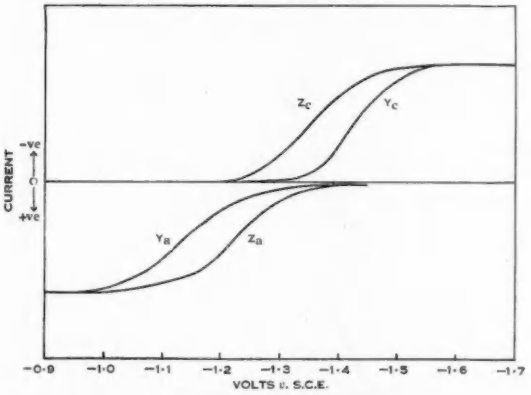

Fig. 4.—Diagrammatic sketch of the effect of a superimposed A.C. on the D.C. anodic and cathodic curves of zinc amalgam. The Y_c and Y_a curves are correctly positioned on the D.C. axis for sodium hydroxide solution.

A process of a somewhat different type occurs when adsorbed non-reducible films interfere with the passage of ions to the drop, or atoms to the solution (Breyer and Hacobian 1952). This is illustrated by the behaviour of $1 \cdot 0 \times 10^{-3}$M Cd^{++} in $1 \cdot 0 \times 10^{-1}$M KCl with various quantities of *cyclo*hexanol present. In this case the electrode process is essentially reversible in the absence of *cyclo*hexanol but becomes increasingly irreversible, as shown in Figure 5, by the separation of the *Y* and *Z* curves and the movement of the cross-over point, as the *cyclo*hexanol concentration is increased.

The irreversibility induced into the system by the *cyclo*hexanol is due to the greater difficulty experienced by the anodic dissolution compared to the cathodic deposition process. In other words, it is easier to deposit ions from the solution into the drop, than to reform ions and transport these to the bulk of the solution.

The following is a possible explanation of this effect : the *cyclo*hexanol forms an adsorbed film on the surface of the drop (Breyer and Hacobian loc. cit.).

When Cd^{++} ions are reformed at the mercury surface some may be attracted to the negative end of the *cyclo*hexanol dipole, which is itself attracted to the mercury drop at these potentials. Its movement to the bulk of the solution is hindered by

(i) the attraction of the *cyclo*hexanol to the drop, and

(ii) the slower movement of the $Cd(cyclohexanol)_n^{++}$ ion ;

compared with the probably more mobile $Cd(H_2O)_m^{++}$ ion. That is, (*a*) due to the small concentration of the *cyclo*hexanol in the bulk of the solution the probability of forming $Cd(cyclohexanol)_n^{++}$ ions is small and the discharge process therefore consists of the discharge of $Cd(H_2O)_m^{++}$ ions ; (*b*) due to the large concentration of *cyclo*hexanol at the surface of the drop the probability of forming $Cd(cyclohexanol)_n^{++}$ ions is large, and the anodic process therefore

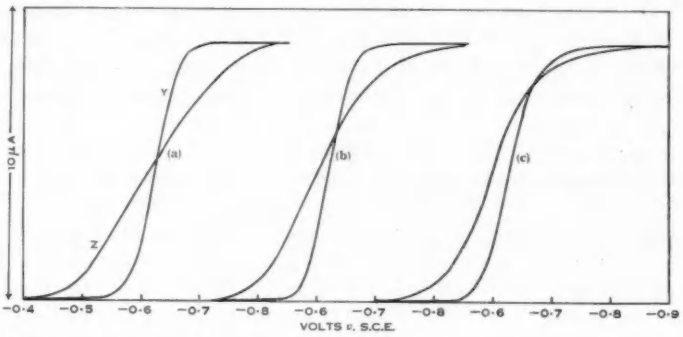

Fig. 5.—The effect of concentration of *cyclo*hexanol on the separation of the *Y* and *Z* curves for $1{\cdot}0\times10^{-3}$M Cd^{++} in $1{\cdot}0\times10^{-1}$M KCl. A.C. = 100 mV 30 c/s. $T = 25$ °C, $m = 2{\cdot}56$ mg sec^{-1}, $t = 3{\cdot}47$ sec. Curve (*a*) $1{\cdot}0\times10^{-2}$M *cyclo*hexanol, curve (*b*) $2{\cdot}0\times10^{-2}$M *cyclo*hexanol, curve (*c*) $4{\cdot}0\times10^{-2}$M *cyclo*hexanol. The solutions were air-free.

consists of the formation of these ions and their transport to the bulk of the solution. The second process would be expected to lag the A.C. field to a greater extent than the first and so cause rectification, the extent of which increases with the *cyclo*hexanol concentration.

It would be reasonable to expect that if the A.C. field varied slowly, that is, if low frequencies were used, then process (*b*) would be able to follow the field to the same extent as process (*a*). Table 2 gives the values of the cross-over potential (E_{co}) for different frequencies for $1{\cdot}0\times10^{-3}$M Cd^{++} in $1{\cdot}0\times10^{-1}$M KCl with $2{\cdot}0\times10^{-2}$ *cyclo*hexanol, and a sweep voltage of 100 mV r.m.s. The values of E_{co}, when plotted against the log of the frequency, gave a straight line. It will be observed that at low frequencies the extent of rectification is less than at high frequencies. This seems to support the suggestion above, that the Cd^{++} ion has, as it were, different mobilities in the anodic and cathodic process. However, if the *cyclo*hexanol concentration is increased, then even at 5 c/s the E_{co} still does not coincide with the D.C. $E_{\frac{1}{2}}$, indicating that the increased

concentration of *cyclo*hexanol at the surface of the drop has resulted in an increased proportion of Cd^{++} ions solvated by the *cyclo*hexanol. This will further decrease the number of Cd^{++} ions transported to the bulk of the solution in the positive half-cycle.

TABLE 2

VALUES OF THE CROSS-OVER POTENTIAL E_{co} FOR $1{\cdot}0\times10^{-3}$M Cd^{++} IN $1{\cdot}0\times10^{-1}$M KCl AND $2{\cdot}0\times10^{-2}$M *cyclo*HEXANOL FOR DIFFERENT FREQUENCIES

$T=25$ °C: reversible $E_{\frac{1}{2}}=0{\cdot}622$ V

Cross-over potential E_{co} (V)	0·623	0·629	0·633	0·641	0·649	0·655
Frequencies (c/s) ..	15	30	60	120	240	480

It is obvious from the results described above that further study of the effect of an applied alternating voltage on D.C. polarograms will yield significant information on the mechanism of the processes occurring at the D.M.E.

Further work is continuing on both reversible and irreversible cases.

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THE OSCILLATING JET METHOD FOR THE MEASUREMENT OF SURFACE TENSION

By K. L. Sutherland*

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Summary

The oscillating jet method for determining the surface tension of pure liquids is shown to give results which are usually low by about 1 per cent. There is moreover no satisfactory criterion to enable a suitable jet to be chosen, results sometimes being low by 4 per cent. A simple procedure, replacing a more complicated one due to Addison (1943, 1945) enables the method to be used for measuring relative surface tensions of pure liquids.

I. Introduction

Of the methods which may be used to measure the surface tension of a freshly generated surface, the oscillating jet method is held to be the most accurate. Rayleigh (1879) and subsequently Pedersen (1906–7), Bohr (1908–9), and Stocker (1920) formulated the theory of the method and described methods for the measurement of surface tension by such jets. The method has also been used by Addison (1943, 1945) in an empirical fashion.

The objects of the present paper are, firstly, to present an account of an experimental method which is more convenient and more accurate than those previously described; secondly, to apply the method as an absolute one to the determination of the surface tension of liquids other than water; and thirdly, to examine an empirical formula, proposed by Addison (1943), for the calculation of surface tensions from measured data. Some interest has been evinced in the method since Rideal and Sutherland (1952) showed that surface tensions of *solutions* of surface-active solutes were dependent upon the particular jet used; although this behaviour probably arises from diffusion and hydrodynamical transport of solute to a surface, it seemed desirable to examine the method itself using pure liquids of accurately known surface tension.

II. Theory of the Oscillating Jet

The theoretical treatment of Bohr (1908–9) is used. If a jet is produced from a tube of elliptical section the surface executes a simple vibration about a cylinder. The surface tension γ is calculated from

$$\gamma = \frac{2\pi(\delta+\rho)r^3U^2J_2\left(\frac{2\pi ir}{\lambda}\right)\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)}{\left(3+\frac{4\pi^2r^2}{\lambda^2}\right)ir\lambda J_2'\left(\frac{2\pi ir}{\lambda}\right)} \times\left[1+2\left(\frac{\eta\lambda}{\pi\delta Ur^2}\right)^{3/2}+\left(\frac{\eta\lambda}{\pi\delta Ur^2}\right)^2+\ldots\right], \quad \ldots. \quad (1)$$

* Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

where δ = density of liquid comprising the jet,
ρ = density of air or surrounding medium,
r = radius of jet (see below),
U = average velocity of jet,
$J_2(x)$, $J_2'(x)$ = second order Bessel functions and derivative respectively,
b/r = amplitude of the jet (see below),
$i = \sqrt{-1}$,
λ = wavelength of the oscillation,
η = coefficient of viscosity of the liquid.

The amplitude b/r is defined by

$$\frac{b}{r} = \frac{r_m - r_i}{r_m + r_i}, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where r_m = maximum radius (major axis) of the jet,
r_i = minimum radius (minor axis) of the jet,

and the stream radius is defined by

$$r = \tfrac{1}{2}(r_m + r_i)\left(1 - \frac{1}{6}\frac{b^2}{r^2}\right). \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

For liquids whose viscosity is not greater than 0·01 poise and for the experimental conditions used herein the correction due to the term in square brackets in equation (**1**) is of the order of 1 part in 1000. This factor is nearly constant for the liquids measured and will be expressed by ψ.

The expansion of the Bessel functions by an asymptotic expression gives

$$\gamma = \frac{4\pi^2(\delta+\rho)U^2r^3\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)\psi}{\lambda^2\left[6+10\left(\frac{\pi r}{\lambda}\right)^2+2\cdot5\left(\frac{\pi r}{\lambda}\right)^4\right]}. \quad \ldots\ldots\ldots\ldots \quad (4)$$

Higher terms in the series contribute less than 1 part in 10,000 to the value of γ.

Bohr (1908–9) has shown that the velocity of the stream U may be calculated from the radius of the jet and the weight W of liquid flowing from the orifice in time t:

$$U = \frac{W}{\pi r^2 \delta t}. \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

The error is less than 0·1 per cent. for the water jets which he examined. Hence equation (**4**) becomes

$$\gamma = \frac{4(\delta+\rho)W^2\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)\psi}{\delta^2t^2\left(6r\lambda^2+10\pi^2r^3+2\cdot5\frac{\pi^4r^5}{\lambda^2}\right)}. \quad \ldots\ldots\ldots\ldots \quad (6)$$

SURFACE TENSION BY THE OSCILLATING JET

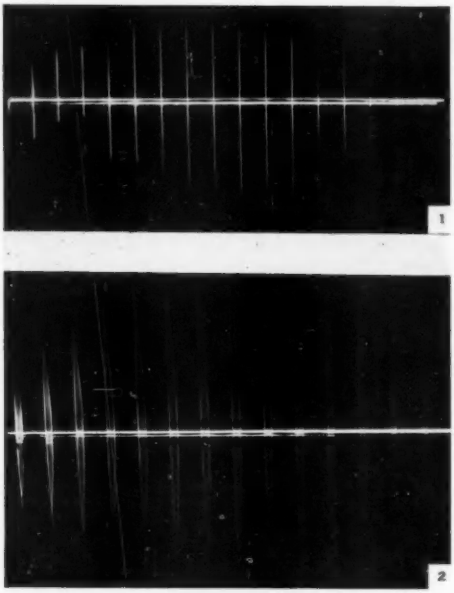

Fig. 1.—Focused images used in measuring wavelength.
Fig. 2.—Unfocused images used for determining the symmetry of the stream.

The quantities to be measured are W, r, b, t, and λ.

In deriving equation (1) it is assumed that:

(i) The fluid is in laminar flow.

(ii) All initial disturbances caused by ejection of liquid from the orifice are absent in that portion of the jet which is measured.

(iii) The vibrational components of velocity of the jet are sufficiently small that second and higher order terms are negligible.

(iv) The viscosity at the surface of the jet is the same as that in the interior of the jet.

(v) The diameter of the jet is small compared with the wavelength of the oscillation.

(vi) The effect of amplitude on the frequency of oscillation may be calculated in the absence of viscous forces.

(vii) The only effect of the surrounding medium is its inertia.

III. Experimental

The orifice was produced by sealing a short length of capillary tubing of elliptical section to tubing of 5 mm internal diameter, then cutting with a glass knife at between 1 and 2 mm from the contraction. The orifice was left untouched. If no irregularities were visible under the microscope the orifice was further tested by forcing water through it; any jet which did not give at least a dozen oscillations was rejected. The symmetry of the jet was checked by the methods of Bohr (1908–9) and Stocker (1920).

(*a*) *Radius and Amplitude*

To measure the radius and amplitude, the stream and three cylinder gauges were photographed on a process plate using a parallel beam of monochromatic light. Distortion induced by the camera lens across the portion of the field used was less than 0·05 per cent. The focal length of the lens (20 cm) was sufficiently large to avoid errors in magnification due to the displacement of the stream behind or in front of the gauges. The stream was placed within 0·2 mm of the plane of the three gauges. A simple autocollimating device was used to place the camera plate perpendicular to the light and parallel to the gauges and stream. The orifice tube was rigidly linked to the gauges to prevent relative movement of the systems.

Photographs showed sharp diffraction bands on the edges of the images. The diameters of the stream and gauge on the plate were measured to the edge of the first diffraction band and the stream diameter calculated. The greatest deviation on test objects was 0·3 per cent. and the mean diameter determined from three values always agreed within 0·1 per cent. with that of the test object.

(*b*) *Outflow Rate*

An electrically operated shutter allowed the jet of liquid to flow into a weighed container for a measured time. The design was that of Stocker (1920). Evaporation from the jet was proved negligible by altering the distance between orifice and container. To avoid constant level reservoirs which are extravagant

in their use of liquid, a falling head was used. A mean outflow rate was determined (variation in head was from 1200 to 1196 mm).

Both the shutter and the timing mechanism were operated by a single switch. The timing unit* was a mechanical counter, counting impulses from a Tinsley 50 cycle tuning fork. The frequency of the fork (49·97 c/s) was determined at the National Physical Laboratory, England. The corrections due to time lags in the relay and in the counter were determined with a scale-of-ten electronic counter governed by a Sullivan tuning fork (200·000 c/s at 18 °C/760 mm pressure). The correction was $0{\cdot}03 \pm 0{\cdot}03$ sec and for the time measured (about 40 sec) the uncertainty was only 0·08 of 1 per cent. This was confirmed by measurements of outflow rate from the same level in the reservoir, for example,

0·3202	0·3205	0·3206	0·3198	0·3204
0·3201	0·3197	0·3201	0·3202	0·3206

The mean value of 0·3202 g sec^{-1} has a probable error of 0·06 of 1 per cent.

Weighings were not in error by more than 0·01 of 1 per cent.

(*c*) *Measurement of Wavelength*

In this measurement the stream of liquid was illuminated by a narrow collimated beam of light. The stream acting as a cylindrical lens produced astigmatic images of a point source (Stocker 1920). The oscillations of the stream are damped so that the focal lengths of the "lenses" increased with distance from the orifice. To obtain sharp images the photographic plate was inclined at an angle θ to the stream. Figure 1 showed the arrangement to measure θ. The collimated beam (adjusted by the usual methods (Glazebrook 1923)) from slit *D* fell on the photographic plate held by a carriage *F* on which angles could be measured to $\pm 1'$ of arc. The instrument was calibrated to $\pm 0{\cdot}5'$. The axis of rotation of the photographic plate was adjusted perpendicular to the collimated beam by usual methods. The angle between beam and plate was determined by replacing the plate with a plane mirror. When perpendicular to the beam the light reflected from the silvered surface fell on the pinhole *P*. The coincidence was observed through a part of the mirror which was left unsilvered. The error of adjustment was $\pm 0{\cdot}5'$. This gave the angle θ_1 between plate and the direction perpendicular to the light. The angle θ_2, between stream and light, was measured by means of an auxiliary optical flat *K*. The lower jaw *H* of the slit was opened and the flat, silvered on the lower portion, was adjusted perpendicular to the beam with screws *I'*, *I''*, and *J*. A slip gauge was then wrung to the surface of the flat to provide a projecting surface parallel to *K*. The jet had been placed as close as possible to the gauge and the distance between gauge and centre of the stream measured with a microscope at two points. From these data the angle between flat and stream could be computed with an error of less than 2'.

* The author is indebted to Mr. S. E. Powell of the Division of Industrial Chemistry for design of the mechanical counter.

Finally the gauge was removed, the slit narrowed to illuminate the stream only, and the images focused on the plate. The focused and unfocused images are shown in Plate 1, Figures 1 and 2. Large photographic plates were used to avoid shifts of the image due to distortion of the gelatin near the edges of a developed plate. The distance between images, l cm, was measured with a Gaertner travelling microscope to within $\pm 0{\cdot}0002$ cm. The wavelength is

$$\lambda = l \cos \theta = l \cos (\theta_1 + \theta_2). \quad \ldots\ldots\ldots\ldots \quad (7)$$

(*d*) *Other Equipment*

All equipment was housed in a constant temperature room (20 ± 1 °C) on a support which was reasonably free from vibration.

Measurements of the surface tension at static surfaces were made by the ring method following the procedure of Harkins and Hubert (1930) and using

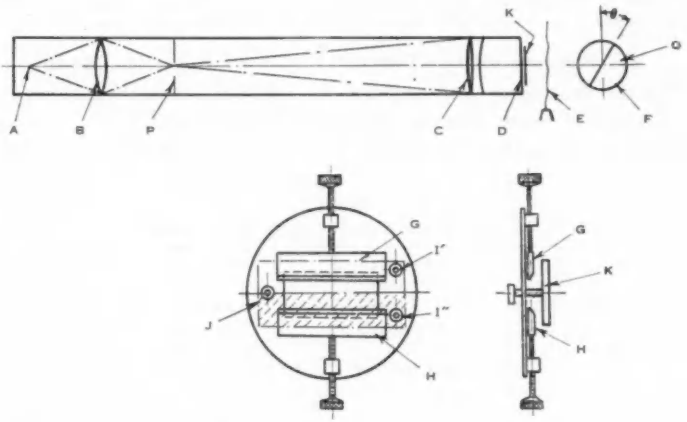

Fig. 1.—Experimental arrangement for the measurement of wavelength.

their correction tables. The platinum-iridium wire of the ring was $0{\cdot}0630 \pm 0{\cdot}0005$ cm diameter and formed into a ring of $2{\cdot}685 \pm 0{\cdot}002$ cm diameter. Reproducibility was of the order of 1 part in 1500.

(*e*) *Purification of Liquids*

The water was twice distilled from acid permanganate solution using a large splash head. The benzene was refluxed with mercuric acetate, shaken with concentrated sulphuric acid, washed with water, dried over calcium chloride, thrice recrystallized by freezing, and fractionally distilled from sodium metal. From a mass spectrographic analysis the only impurities found were 1 part each of toluene and thiophene in 3000 parts of benzene.

The carbon tetrachloride was shaken with three changes of ethanol containing potassium hydroxide. After washing five times with distilled water and drying overnight with potassium hydroxide, the material was fractionally distilled. The physical constants are shown in Table 1.

TABLE 1

PHYSICAL CONSTANTS OF LIQUIDS INVESTIGATED

Substance	Boiling Point (°C) (corr.)	Refractive Index (Na D line)	Surface Tension* (20 °C dyn cm^{-1})
Benzene	80·1 (80·12)†	1·5044 (1·5044)	28·89 (28·88)
Carbon tetrachloride ..	76·73 (76·71)	1·4609 (1·4604)	26·72 (26·77)
Water	100·00 (100·00)	—	72·8 (72·75)

* Measured by the ring method.

† Values in brackets are from the International Critical Tables (1928) or Mulliken and Huntress (1941).

IV. Results of the Determination of Surface Tension

The determinations are recorded in Table 2. Results at temperatures other than 20 °C were corrected to this temperature using the temperature coefficients given in the International Critical Tables (1928).

TABLE 2

MEASURED DATA AND CALCULATED SURFACE TENSIONS

Substance	No.	Jet	$W/\delta t$ (cm^3 sec^{-1})	b/r (mean)	r (cm)	λ (cm)	t (°C)	Surface Tension (dyn cm^{-1})	
								t °C	20·0 °C
Water ..	1	*A*	0·3634	0·076	0·01715	0·2577	19·5	72·40	72·47
	2	*A*	0·8555	0·115	0·01711	0·6315 to 0·6233	20·4	72·48	72·54
	3	*A*	0·3707	0·075	0·01713	0·2638	21·4	72·30	72·51
	4	*A*	0·5135	0·099	0·01712	0·5269 to 0·5225	20·5	72·31	72·38
	5	*K*	1·0969	0·037	0·03094	0·5860	20·5	72·21	72·28
	6	*K*	0·8560	0·025	0·03097	0·4506	20·0	72·38	72·38
	7	*E*	0·3211	0·069	0·01637	0·2335	20·5	72·1	72·2
	8	*E*	0·3205	0·069	0·01637	0·2328	20·5	72·0	72·0
	9	*L*	0·6887	0·024	0·02584	0·4067	19·1	69·3	69·5
	10	*L*	0·6949	0·024	0·02586	0·4113	20·1	69·4	69·4
	11	*L*	0·6949	0·024	0·02583	0·4095	20·1	69·7	69·7
Benzene ..	12	*A*	0·3860	0·096	0·01709	0·4190	19·9	28·71	28·70
	13	*A*	0·3899	0·096	0·01710	0·4210	20·1	28·50	28·51
Carbon tetrachloride ..	14	*A*	0·3829	0·090	0·01723	0·5895	19·8	26·70	26·67

The mean values and those given in the *International Critical Tables* (I.C.T.) are listed in Table 3.

TABLE 3

COMPARISON OF SURFACE TENSION OF WATER, CARBON TETRACHLORIDE, AND BENZENE

Temperature 20·0 °C

Liquid	Surface Tension (dyn cm^{-1})	References
Water (jet *A*) ..	72·48±0·10	Present work
Water (jet *E*) ..	72·1 ±0·2	" "
Water (jet *K*) ..	72·33±0·10	" "
Water (jet *L*) ..	69·5 ±0·3	" "
Water	72·75±0·05	I.C.T.
Benzene (jet *A*) ..	28·61±0·1	Present work
Benzene	28·88±0·05	I.C.T.
Carbon tetrachloride ..	26·67±0·1	Present work
Carbon tetrachloride ..	26·77±0·1*	I.C.T.
	26·95±0·1†	

* Against air.

† Against saturated vapour.

Bohr (1908–9) obtained the following mean values for water, which are corrected to 20 °C in the last column :

Jet	Number of Determinations	12·0 °C	20·0 °C
		(dyn cm^{-1})	
I	3	73·33	72·15
II	3	73·08	71·90
III	2	73·37	72·19
IV	2	73·15	71·97

and Stocker (1920) the following mean values for water :

Jet	Number of Determinations	18·0 °C	20·0 °C
		(dyn cm^{-1})	
I	14	72·52	72·22
II	2	72·31	72·01

If we accept the values given in the *International Critical Tables*, it is apparent that measurements by the oscillating jet method give results which are usually low by between 1 and $\frac{1}{3}$ of 1 per cent. Results from jet *L* in particular indicate that consistent results are possible with a jet which satisfies all the preliminary tests but from which the calculated surface tensions prove to be 4 per cent. too low.

No correlation could be traced between radius, amplitude of jet, viscosity or density of the liquid, and the surface tension measured on a particular jet. In those tests (Table 2, experiments 2 and 4) in which the wavelength varied considerably along the jet, the amplitude correction $(1+37b^2/24r^2)$ was just sufficient to remove the variation. This is important for it indicates that this term in the theoretical treatment is essentially correct. The viscosity correction (term ψ of equation (4)) is very small.

The effect of electric charges on the jet, which could cause an apparent decrease in surface tension, was tested. By applying a voltage of 10 times the amount found between the orifice and end of the jet the effect was shown to be less than 1 part in 4000.

The conclusion may be drawn that the method is not suitable for an accurate absolute determination of the surface tension of a pure liquid. Even the relative values do not agree to better than $\frac{1}{2}$ per cent.

V. A Study of Addison's Method of Calculation of Surface Tension from the Oscillating Jet

The purpose of Section V is to examine results obtained by Addison using an empirical formula to deduce the surface tension. This formula applies accurately to his jet, for measurement of the surface tension of 10 liquids gave results in good agreement with accepted values (Addison 1943).

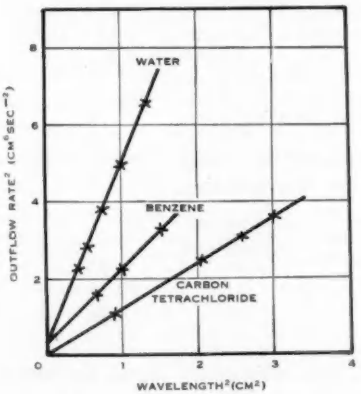

Fig. 2.—Variation of wavelength with outflow rate (data after Addison 1943).

Addison's (1943, 1945) data were first examined to determine the applicability of the Bohr equation. For his jet the terms $2\cdot5(\pi^4r^5/\lambda^2)$ and ψ (see equation (**6**)) would contribute less than $0\cdot2$ per cent. to the calculated surface tension. Equation (**6**) then becomes

$$\gamma=\frac{4(\rho+\delta)W^2\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)}{\delta^2t^2(6r\lambda^2+10\pi^2r^3)}. \quad \ldots\ldots\ldots\ldots \quad (8)$$

The orifice used by Addison had a small eccentricity and consequently the amplitude term would be less than 1 per cent.

Figure 2 shows graphs of W^2/δ^2t^2 against λ^2 for Addison's (1943) results. Since r and b/r should be approximately constant a linear relation between the above variables is expected and found. A straight line fitted all points with a

deviation of less than 1 per cent. Identity of the equation describing Addison's data, namely,

$$\frac{W^2}{\delta^2 q^2} = p\lambda^2 + q, \qquad \text{..... (9)}$$

with equation (8) requires that

$$\left.\begin{aligned} p &= \frac{3r\gamma}{2(\rho+\delta)\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)}, \\ q &= \frac{5\pi^2 r^3\gamma}{2(\rho+\delta)\left(1+\frac{37}{24}\frac{b^2}{r^2}\right)}, \\ r &= \left(\frac{3q}{5\pi^2 p}\right)^{\frac{1}{3}}. \end{aligned}\right\} \qquad \text{..... (10)}$$

and that

Table 4 gives the calculated values of r for his jet.

TABLE 4

CALCULATED RADIUS OF JET

Substance	p	q	r (cm)
Water	4·69	0·396	0·0716
Benzene	2·072	0·213	0·0789
Methanol	1·709	0·265	0·0961
Carbon tetrachloride ..	1·090	0·259	0·1201

Addison (1943, p. 537) states that the radius of the capillary from which he formed the tip was about 0·1 cm. It is only of the same order as that given in the final column of Table 4, where the variation in values of r is enormous. Table 5 shows the results of measurement on jets from our orifice A. The radius varies only by about 1 per cent. It must be deduced that Addison's jet would be unsatisfactory to determine surface tension using the Bohr equation.

TABLE 5

THE JET RADIUS PRODUCED BY ORIFICE A

Liquid	Radius (cm)	
Water	0·01711	Varying rates of flow
Water	0·01715	
Water	0·01712	
Benzene	0·01710	Duplicate
Benzene	0·01709	
Solution of:		
2·03 g 3-methyl-1-butanol/l of water	0·01728	
0·6 g *n*-heptanol/l of water	0·01731	Varying rates of flow
	0·01729	

Attempts to apply Addison's empirical method to jets A and K gave results which were in error by at least 5 per cent. and the application of his formula was always unsatisfactory. Equation (**8**) should prove ample in many measurements of surface tension by the oscillating jet method. It is much simpler to use than Addison's equation, which was designed to avoid extensive computation, and if the radius is not measured then it may be deduced (in so far as it is constant) from measurements at two outflow rates of the one liquid. The amplitude term may be kept small by choosing an orifice of small ellipticity.

VI. Conclusions

It is shown that absolute determinations of the surface tension of water, benzene, and carbon tetrachloride by the oscillating jet method are between $\frac{1}{2}$ and 1 per cent. lower than the accepted values. The determinations on water agree with the measurements made by Bohr and Stocker also using the oscillating jet method.

Jets may be produced which satisfy all the criteria known for satisfactory use, but which record the surface tension as being very much lower than the accepted value. The method is unsatisfactory at present, since the only condition for choice of an orifice is that the jet it produces gives the " right " answer !

For the measurement of surface tension to within a few per cent. a simple equation may be derived from Bohr's equation. The only measurements needed are the outflow rate and the wavelength of the oscillations along the jet.

VII. Acknowledgments

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THE VOLUME CHANGE ON IONIZATION OF WEAK ELECTROLYTES

By S. D. HAMANN* and S. C. LIM*

[*Manuscript received June 25, 1954*]

Summary

The standard partial molar volumes of some strong and weak electrolytes have been measured in water and three other solvents. The results have been used to estimate the volume changes which accompany the ionization of weak electrolytes. Solvent effects are discussed.

I. INTRODUCTION

A number of experiments in this Laboratory (Buchanan and Hamann 1953; Strauss, unpublished data) have shown that the ionization of weak electrolytes is greatly enhanced by an increase in the hydrostatic pressure. The purpose of the work reported here has been to determine the manner in which this pressure effect varies with the chemical structure of the electrolyte and its solvent. We have found this information indirectly from measurements of the standard partial molar volumes $\bar{V}^0$ of each electrolyte in the ionized and un-ionized forms. From the difference $\Delta\bar{V}^0$ between these two volumes, the change of the "thermodynamic" ionization constant K with pressure is given by Planck's (1887) relation

$$-\left(\frac{\partial \log_e K}{\partial p}\right)_{T,\text{conc.}} = \left(\frac{\Delta\bar{V}^0}{RT}\right)_p = \left(\frac{\bar{V}_i^0 - \bar{V}_u^0}{RT}\right)_p, \quad \ldots\ldots\ldots \quad (1)$$

where p is the pressure, effectively one atmosphere in these measurements; T is the absolute temperature, and R is the gas constant. The subscripts i and u denote the ionized and un-ionized states.

The limited ionization of a weak acid or base usually makes it impracticable to find $\bar{V}_i^0$ from the densities of solutions of the acid or base itself; it must be found indirectly from measurements on solutions of some related strong electrolytes. For example, for the acid HA it is given by the relation

$$\bar{V}^0_{H^+A^-} = \bar{V}^0_{H^+Cl^-} + \bar{V}^0_{Na^+A^-} - \bar{V}^0_{Na^+Cl^-}, \quad \ldots\ldots\ldots \quad (2)$$

and for the bases BOR (B is the basic group, R is a hydrogen atom or alkyl group), by

$$\bar{V}^0_{B^+OR^-} = \bar{V}^0_{B^+Cl^-} + \bar{V}^0_{Na^+OR^-} - \bar{V}^0_{Na^+Cl^-}. \quad \ldots\ldots\ldots \quad (3)$$

On the other hand $\bar{V}_u^0$ is given directly by the densities of solutions of the weak electrolytes, if a small correction is applied for the amount of ionization in these solutions.

* Division of Industrial Chemistry, C.S.I.R.O., High Pressure Laboratory, University of Sydney.

II. Results

We define an apparent molar volume for the solute by

$$\varphi = \frac{M}{d_0} - \frac{1000}{c}\left(\frac{d-d_0}{d_0}\right), \quad \ldots\ldots\ldots\ldots\ldots (4)$$

where M is the molecular weight of the solute and c is its molar concentration ; d_0 is the density of the solvent and d is the density of the solution. For very strong and very weak electrolytes we have found $\bar{V}^0$ by measuring φ at several values of c and extrapolating φ to zero concentration, where it becomes equal to $\bar{V}^0$. For weak electrolytes of intermediate strength ($K > 10^{-4}$ g-mol kg^{-1}) allowance was made for the partial ionization of the solute :

$$\varphi_{exp} = (1-\alpha)\varphi_u + \alpha\varphi_i,$$

and so

$$\varphi_u = \frac{\varphi_{exp} - \alpha\varphi_i}{1-\alpha}. \quad \ldots\ldots\ldots\ldots\ldots (5)$$

In these formulae α is the degree of dissociation calculated from the ionization constant and the concentration of the solute, and φ_i can be taken as $\bar{V}_i^0$, found from (**2**) and (**3**). The extrapolations of φ to zero concentration were simplified by the fact that φ varies linearly with c for weak electrolytes and with $c^{\frac{1}{2}}$ for strong electrolytes.

The results of these measurements, together with some earlier data, are given in Tables 1 to 4.

Table 1

Ionization of bases in water at 25 °C

$BOH \rightleftharpoons B^+ + OH^-$

All volumes are in cm^3 g-mol^{-1}

Base	$\bar{V}^0_{BOH}$	$\bar{V}^0_{B^+Cl^-}$	$\bar{V}^0_{B^+OH^-}$ *	$\Delta\bar{V}^0$
Ammonium hydroxide†	42·6	36·0	12·6	—30·0
Methylammonium hydroxide ..	59·6	55·5	32·1	—27·5
Dimethylammonium hydroxide ..	77·1	73·1	49·7	—27·4
Trimethylammonium hydroxide ..	96·4	91·7	68·3	—28·1
Anilinium hydroxide	107·1	101·9	78·5	—28·6
Pyridinium hydroxide	95·2	90·5	67·1	—28·1
Piperidinium hydroxide	108·2	107·3	83·9	—24·3

* Found from the values in the previous column by adding

$$\bar{V}^0_{OH^-} - \bar{V}^0_{Cl^-} = -5\cdot3,\ -18\cdot1 = -23\cdot4,\ \text{cm}^3\ \text{g-mol}^{-1}$$

(Owen and Brinkley 1941).

† The densities of ammonium hydroxide and chloride solutions were taken from the *International Critical Tables* (for 20 °C).

III. Discussion

The values in Table 1 indicate that the volume change for the ionization of bases varies only slightly with their structure. The acids in Table 2 show much greater effects but there seems to be no simple explanation for this.

There is a very large decrease in $\Delta\bar{V}^0$ when the solvent is changed from water to methanol. This is apparent in the values for the ionization of pyridine and piperidine in water (Table 1) and in methanol (Table 3). The decrease is due to the smaller effective volumes of ions in methanol, shown also by the data

TABLE 2

IONIZATION OF ACIDS IN WATER AT 25 °C

$HA \rightleftharpoons H^+ + A^-$

All volumes are in $cm^3\ g\text{-}mol^{-1}$

Acid	$\bar{V}^0_{HA}$	$\bar{V}^0_{Na^+A^-}$	$\bar{V}^0_{H^+A^-}$*	$\Delta\bar{V}^0$
Water†	18·1	—6·8	—5·3	—23·4‡
Formic Acid	34·1	24·8	26·3	—8·0
Acetic Acid	52·0	38·0	39·5	—12·5 (—9·2)‡
Propionic Acid	67·9	52·7	54·2	—13·7
Butyric acid	84·7	69·5	71·0	—13·7
Carbonic acid†	53·0	22·5	24·0	—29·0‡
Phenol	86·0	67·5	69·0	—17·0
Phosphoric acid†	—	—	—	—16·2§

* Found from the values in the previous column by adding

$$\bar{V}^0_{H^+} - \bar{V}^0_{Na^+} = +1{\cdot}5,\ cm^3\ g\text{-}mol^{-1}$$

(Owen and Brinkley 1941).

† 1st dissociation.

‡ From Owen and Brinkley (1941).

§ Smith (1943).

in Table 4. It is known that the solvent in the immediate neighbourhood of an ion is in a state of compression (Zwicky 1925) and we might therefore reasonably expect that the volume increase accompanying the introduction of ions into a

TABLE 3

IONIZATION OF BASES IN METHANOL AT 25 °C

$BOCH_3 \rightleftharpoons B^+ + OCH_3^-$

All volumes are in $cm^3\ g\text{-}mol^{-1}$

Base	$\bar{V}^0_{BOCH_3}$	$\bar{V}^0_{B^+Br^-}$	$\bar{V}^0_{B^+OCH_3^-}$*	$\bar{V}^0$
Pyridinium methoxide	118·9	71·3	65·5	—53·4
Piperidinium methoxide	134·9	91·2	85·4	—49·5

* Found from the values in the previous column by adding

$$\bar{V}^0_{Na^+OCH_3^-} - \bar{V}^0_{Na^+Br^-} = -0{\cdot}7,\ -5{\cdot}1 = 5{\cdot}8,\ cm^3\ g\text{-}mol^{-1}$$

(present paper).

liquid should vary inversely as the compressibility of the liquid. In Table 5 we list the difference between the partial molar volumes of ions in water and in non-aqueous solvents, together with the compressibilities of the solvents at atmospheric pressure and room temperature.

TABLE 4

SALTS IN VARIOUS SOLVENTS AT 25 °C

$\bar{V}_i^0$ in cm³ g-mol⁻¹

Salt	Solvent				
	Water	Methanol	Ethanol	Glycol	Acetic Acid
LiBr	24·0*	5·7†	—	22·5†	—
NaBr	23·5*	5·1	—	28·0†	—
NaI	35·1*	16·2†	—	38·4†	—
KI	45·3*	21·5‡	—	47·8†	—
NH_4NO_3	47·2*	31·0	—	—	—
Piperidinium Br ..	114·2	91·2	100·4	—	103·1

* Owen and Brinkley (1941).

† Gibson and Kincaid (1937).

‡ MacInnes and Dayhoff (1953).

The data are displayed in Figure 1 which shows that there is a remarkably good correlation between the ionic molar volumes and the solvent compressibilities.

TABLE 5

Solvent (*S*)	Glycol	Water	Acetic Acid	Ethanol	Methanol
Compressibility, $-\frac{1}{V}\left(\frac{\partial V}{\partial p}\right) \times 10^6$ atm	34*	44†	96‡	111†	136†
$(\bar{V}_i^0)_S - (\bar{V}_i^0)_{H_2O}$/cm³ g-mol⁻¹§ ..	+2	0	−11	−14	−20

* Measurements by Bridgman (1931).

† Quoted by Bridgman (1949).

‡ Measurements by Venkateswaran (1927).

§ Mean values from Table 4 of the present paper.

IV. EXPERIMENTAL

(*a*) *Method*

The method of density measurement has been described in detail by Prince (1953). The densities of the solutions were measured in 10 ml Sprengel-Perkin pyknometers held at 25±0·01 °C in a water thermostat tank. The usual buoyancy corrections were applied to all the weighings.

Three or four concentrations of each solute between 0·1 molal and molal were examined and each density was measured in duplicate. The densities

could be reproduced to within $\pm 0 \cdot 00005$ g cm^{-3}, corresponding to an uncertainty of not more than $\pm 0 \cdot 5$ cm^3 g-mol^{-1} in φ. The solutions were made up by weight unless it is otherwise indicated below.

(*b*) *Materials*

(i) *Solvents.*—(1) *Water.* Conductivity water was used to calibrate the pyknometers and in making up all the aqueous solutions.

(2) *Methanol.* Commercial methanol was carefully dried and fractionated. The final product had a density of 0·7866–0·7867 g cm^{-3} at 25 °C.

(3) *Ethanol.* A purified sample of ethanol was kindly supplied by Mr. I. Brown, Division of Industrial Chemistry, C.S.I.R.O., Melbourne. Its density, when used, was 0·7853 g cm^{-3} at 25 °C.

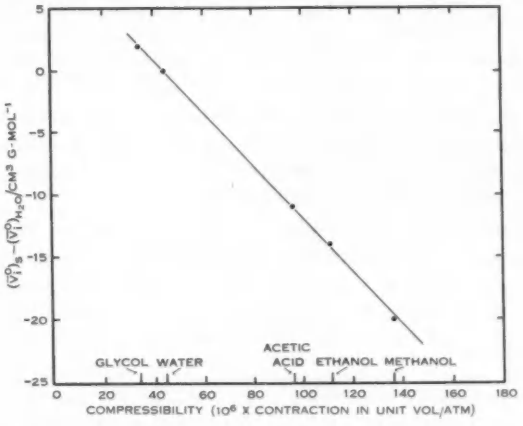

Fig. 1.—Partial molar volumes of ions in various solvents.

(4) *Acetic Acid.* Some pure acetic acid (m.p. 16·55 °C) was given to us by Mr. R. G. H. Prince of the Chemical Engineering Department of the University of Sydney.

(ii) *Solutes.*—(1) *Sodium Bromide and Ammonium Nitrate.* These were analytical grade reagents, dried at 110 °C and cooled in a vacuum desiccator.

(2) *The Hydrochlorides of Methylamine, Dimethylamine, and Trimethylamine.* Commercial samples of these salts were recrystallized from water and dried *in vacuo* over phosphorus pentoxide.

(3) *Methylamine, Dimethylamine, and Trimethylamine.* Solutions of these amines were prepared directly by boiling solutions of the hydrochlorides with potassium hydroxide and barium chloride and passing the vapours through a spray trap into conductivity water. The solutions were standardized against hydrochloric acid.

(4) *Aniline, Pyridine, and Piperidine.* The commercial products were dried by potassium hydroxide and carefully fractionated. The boiling points were correct.

(5) *Aniline Hydrochloride and Pyridine Hydrochloride.* A weighed amount of the base was dissolved in conductivity water and neutralized by standard hydrochloric acid using an external indicator. The amount of acid required provided a check on the purity of the bases.

(6) *Pyridine Hydrobromide and Piperidine Hydrobromide.* The method of preparation was similar to that just described. The salts were crystallized from water and acetone and dried in a vacuum desiccator over phosphorus pentoxide.

(7) *Formic Acid.* About 100 ml of 95% acid was obtained from 1 l. of commercial formic acid after three fractional crystallizations. The actual concentration of formic acid in solutions of this acid was found by titration against sodium hydroxide.

(8) *Propionic Acid, Butyric Acid, and Phenol.* The commercial products were purified by fractional distillation.

(9) *Sodium Salts of Formic, Acetic, Propionic, and Butyric Acids and of Phenol.* These were all prepared in solution by neutralizing known weights of the acids with standard sodium hydroxide (this provided a check on the purity of the acids) using an external indicator.

(10) *Sodium Methoxide.* Metallic sodium was dissolved in pure methanol. The concentration of the solution was found by titration against standard hydrochloric acid.

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THE MECHANISM OF THE CANNIZZARO REACTION OF FORMALDEHYDE

By R. J. L. Martin*

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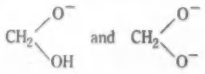
Summary

For a wide range of concentrations of formaldehyde and alkali, the Cannizzaro reaction of formaldehyde can be described as the sum of a third and a fourth order reaction. However, the concentrations which are used for the rate equations must be corrected for the amount of methylene glycol anion present. The dissociation constant of methylene glycol as determined from the kinetic data is the same magnitude as that derived electrometrically. The mechanism of the reaction is interpreted as a reaction between formaldehyde and the hydride ion donors



It is shown why the third order reaction proposed by previous workers is not always applicable.

I. Introduction

Formaldehyde and certain other aldehydes, such as the aromatic and tertiary aliphatic, undergo with hydroxyl ions a Cannizzaro reaction, in which two molecules of aldehyde disproportionate to form one molecule each of alcohol and acid :

$$2RCHO + OH^- \rightarrow RCH_2OH + RCOO^-.$$

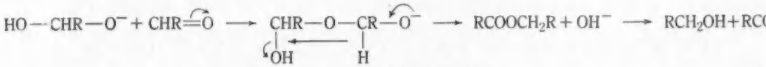
A considerable amount of work has been done on the kinetics of this reaction and it has been shown to be either third or fourth order, although in some cases there is doubt as to which is correct (Geib 1934 ; Molt 1937 ; Eitel and Lock 1939 ; Eitel 1942 ; Tommila 1942).

Over a very limited range of concentrations of formaldehyde and alkali, Birstein and Lobanov (1927), Pajunen (1950), and Pfeil (1951) have shown that the reaction is third order. Euler and Lövgren (1925) have shown the reaction to be bimolecular with respect to formaldehyde at a constant pH. These workers corrected for the amount of methylene glycol anion present and concluded that the mechanism involved the reaction between two methylene glycol anions, that is, the reaction is fourth order.

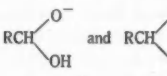
The kinetic evidence and the mechanism of the reaction have been discussed by Hammett (1946, p. 350), Dewar (1949, p. 130), Remick (1949, p. 473), Alexander (1950, p. 168), and Ingold (1953, p. 704).

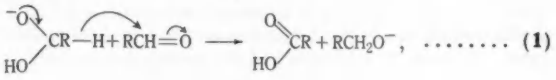
* Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

One mechanism which has received much support is that the aldehyde hydrate anion reacts with the aldehyde to form a hemiacetal, which rearranges and hydrolyses as shown in the following sequence of reactions :

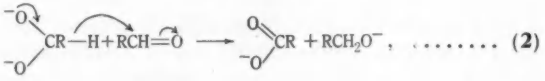


The concentration of aldehyde hydrate anion was assumed to be very small and proportional to $[RCH{=}O][OH^-]$ and the reaction would therefore be third order.

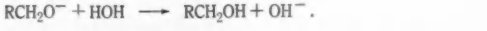
Ingold (1953) gives reasons for believing that this mechanism is improbable and alternatively suggests a reaction between the aldehyde and the hydride ion donors  and .



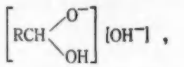
(1)



(2)



If the concentration of the doubly charged anion is small and proportional to



the reaction would then become the sum of a third and a fourth order reaction. Hammett was the first to suggest that the mechanism consisted of a reaction between the doubly charged anion and the aldehyde, that is, the reaction is fourth order.

In this investigation it is shown that the concentrations of the reactants must be corrected for the amount of methylene glycol anion present. It is shown, for a wide range of concentrations of formaldehyde and alkali, that the reaction is not third order as found by previous workers, but is the sum of a third and fourth order reaction. The dissociation constant of methylene glycol has been estimated from the kinetic data and is the same magnitude as that derived from electrical measurements.

II. Discussion

The results in Table 1 show that an extremely good set of calculated third order velocity constants is obtained within the run. This was also found to be the case by Birstein and Lobanov (1927), Pajunen (1950), and Pfeil (1951), although it must be pointed out that in some cases their constants varied with time.

TABLE 1

THIRD ORDER CONSTANTS FOR THE CANNIZZARO REACTION IN WATER AT 40 °C

Run No. 9 NaOH (0·01505N) CH_2O (0·3644M)		Run No. 16 NaOH (0·4033N) CH_2O (0·0992M)		Run No. 20 NaOH (0·2993N) CH_2O (0·2922M)	
CH_2O Used (%)	k_3 ($\times 10^{-4}$ sec^{-1} g-mol^{-2} l^2)	CH_2O Used (%)	k_3 ($\times 10^{-4}$ sec^{-1} g-mol^{-2} l^2)	CH_2O Used (%)	k_3 ($\times 10^{-4}$ sec^{-1} g-mol^{-2} l^2)
0·33	2·13	8	6·67	2·3	4·35
0·86	1·85	16	6·79	4·6	4·57
1·2	2·06	22	6·62	10	4·46
1·4	1·90	27	6·67	13	4·32
1·7	1·92	33	6·92		
1·9	1·91	40	6·74		
2·1	1·91				

TABLE 2

THIRD ORDER VELOCITY CONSTANTS FOR CANNIZZARO REACTION AT 40 °C IN WATER

Run No.	Ionic Strength	NaOH (g-mol l^{-1})	CH_2O (g-mol l^{-1})	$k_{3obs.}$ ($\times 10^4$ sec^{-1}g-mol^{-2} l^2)
1	0·4153	0·01511	0·2734	2·14
2	0·4157	0·0155	0·2723	2·08
3	0·4256	0·02543	0·2731	2·54
4	0·4265	0·02627	0·2721	2·47
5	0·4265	0·02634	0·2729	2·07
6	0·3996	0·04936	0·2727	3·12
7	0·4099	0·00986	0·3644	1·54
8	0·4094	0·00940	0·3643	1·97
9	0·4153	0·01505	0·3644	2·02
10	0·4256	0·02543	0·3657	2·35
11	0·3993	0·04923	0·3523	2·33
12	0·1012	0·1009	0·1012	4·98
13	0·2021	0·2017	0·0995	6·05
14	0·3024	0·3022	0·0992	6·56
15	0·4042	0·4036	0·0998	6·64
16	0·4042	0·4033	0·0992	6·73
17	0·3024	0·3003	0·1957	5·21
18	0·3024	0·2973	0·1841	5·27
19	0·3024	0·2973	0·1900	5·25
20	0·3024	0·2993	0·2922	4·43
21	0·4046	0·2022	0·2973	3·75
22	0·4046	0·2017	0·2978	3·73
23	0·4046	0·2038	0·0989	6·43
24	0·4043	0·4043	0·0430	6·24
25	0·4041	0·4041	0·01625	7·90
26	0·4023	0·2022	0·01739	8·57

However, if the initial alkali and formaldehyde concentrations are altered over a wide range, it is found that the calculated third order constants vary widely from run to run as shown in Table 2. At the low alkali concentrations, runs No. 1–11, a limiting third order law appears to hold.

The third order equation was derived on the basis of a reaction between the methylene glycol anion and formaldehyde, and it was assumed that the concentration of methylene glycol anion was too small to affect greatly the concentrations of formaldehyde and alkali.

Walker (1953, p. 46) has reviewed the evidence which indicates that formaldehyde exists in aqueous solution as methylene glycol although the solution reacts as formaldehyde $CH_2{=}O$. The equilibrium

$$CH_2{=}O + H_2O \rightleftharpoons CH_2(OH)_2$$

lies well to the right and the concentration of $CH_2{=}O$ will be small and proportional to $[CH_2(OH)_2]$.

The methylene glycol is a weak acid and can ionize in the following way:

$$CH_2(OH)_2 \rightleftharpoons CH_2\begin{matrix}O^-\\OH\end{matrix} + H^+,$$

$$CH_2\begin{matrix}O^-\\OH\end{matrix} \rightleftharpoons CH_2\begin{matrix}O^-\\O^-\end{matrix} + H^+.$$

The first dissociation constant has been measured by Euler and Euler (1905), Euler and Lövgren (1925), Levy (1934), Wadano (1934), Veselý and Brdička (1947), Sauterey (1952), and Martin (1954), and it is possible to correct for the amount of methylene glycol anion present. Since the second dissociation constant of methylene glycol is expected to be at least some factor of 10^3 smaller than the first, the concentration of doubly charged anion will be small and proportional to

$$\left[CH_2\begin{matrix}O^-\\OH\end{matrix}\right][OH^-].$$

Therefore, there are three entities whose concentrations are needed:

$$OH^-,\ CH_2(OH)_2, \text{ and } CH_2\begin{matrix}O^-\\OH\end{matrix}.$$

They are obtained from the equations

$$\left[CH_2\begin{matrix}O^-\\OH\end{matrix}\right] + [OH^-] = a,$$

$$\left[CH_2\begin{matrix}O^-\\OH\end{matrix}\right] + [CH_2(OH)_2] = b.$$

and

$$K_h = [CH_2(\bar{O}H)_2]\ [OH^-] \Big/ \left[CH_2\begin{matrix}O^- \\ OH\end{matrix}\right],$$

which give the relationships

$$[CH_2(OH)_2] = -(a-b+K_h)/2 \pm (\sqrt{(a-b+K_h)^2+4K_hb})/2, \quad .. \quad (3)$$

$$[OH^-] = a-b+[CH_2(OH)_2], \quad ..... \quad (4)$$

where a and b are the total alkali and formaldehyde concentrations and K_h is the hydrolysis constant.

Apart from forming anions, methylene glycol can ionize in the following way :

$$CH_2(OH)_2 \rightleftharpoons {}^+CH_2OH + OH^-,*$$

and the $^+CH_2OH$ should accept hydride ions even more rapidly than $CH_2=O$:

$$\begin{matrix}{}^-O \\ {}^-O\end{matrix}\!\!>\!CH\!-\!H + {}^+CH_2OH \longrightarrow HCOO^- + CH_3OH\,.$$

The rate of the Cannizzaro reaction will then be the sum of the rates of the following reactions, where k_0, k_1', k_1'', and k_2 are the specific rate constants for each reaction.

$$^+CH_2OH + CH_2\begin{matrix}O^- \\ OH\end{matrix} \qquad \text{rate} = k_0\,[CH_2(OH)_2]^2\,,$$

$$^+CH_2OH + CH_2\begin{matrix}O^- \\ O^-\end{matrix} \qquad \text{rate} = k_1'\,[CH_2(OH)_2]^2\,[OH^-]\,,$$

$$CH_2=O + CH_2\begin{matrix}O^- \\ OH\end{matrix} \qquad \text{rate} = k_1''\,[CH_2(OH)_2]^2\,[OH^-]\,,$$

$$CH_2=O + CH_2\begin{matrix}O^- \\ O^-\end{matrix} \qquad \text{rate} = k_2\,[CH_2(OH)_2]^2\,[OH^-]^2\,.$$

Therefore,

$$\text{total rate}/[CH_2(OH)_2]^2 = k_0 + k_1[OH^-] + k_2[OH^-]^2, \quad .... \quad (5)$$

where $k_1 = k_1' + k_1''$.

The value for the dissociation constant of methylene glycol is $2{\cdot}0 \times 10^{-13}$ g-mol l^{-1} at 40 °C (Martin 1954) ; the dissociation constant of water at 40 °C is $2{\cdot}71 \times 10^{-14}$ g-mol l^{-1} (Harned and Hamer 1933) and the hydrolysis constant of

* The existence of the ion $^+CH_2OH$ in strong alkali seems to be indicated from the studies on the xylenol-formaldehyde reaction in which the rate is approximately inversely proportional to the square root of the hydroxyl ion concentration. This can be partly explained as a reaction between the xylenol and the electrophilic reagent $^+CH_2OH$, the concentration of which is small and proportional to $[CH_2(OH)_2]/[OH^-]$ (Martin, unpublished data).

methylene glycol is therefore 0·13 g-mol l^{-1}. Substitution of this value of K_h and the various values of a and b in equations (3) and (4) gives the actual methylene glycol and hydroxyl ion concentrations. Since a regular set of third order velocity constants can be calculated within a run, the total rate $=k_3ab^2$, where k_3 is the third order constant calculated for those particular values of a and b.

In Figure 1 the function, rate/$[CH_2(OH)_2]^2$, is plotted against $[OH^-]$ and according to equation (5) should show a quadratic relationship. From the graph this appears to hold. Since k_0 is the intercept on the vertical axis, it follows from the graph that k_0 is either zero or very small, but certainly negligible.

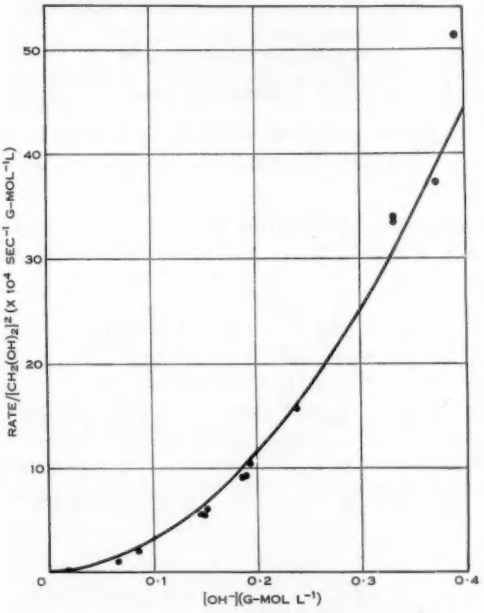


Fig. 1.—Graph of rate/$[CH_2(OH)_2]^2$ against $[OH^-]$ for $K_h=0·13$.

The expression

$$\text{rate}/[CH_2(OH)_2]^2[OH^-]=k_1+k_2[OH^-]$$

therefore replaces equation (5) and gives a linear relation from which k_1 and k_2 can be evaluated by the method of least squares. With the resulting values of k_1 and k_2 the quadratic expression can be calculated, and its graph is the full line shown in Figure 1.

Since the measured value for the dissociation constant of methylene glycol can only be regarded as approximate (Martin 1954), it is of interest to know what effect the value of K_h has on the postulated quadratic relationship.

If we put $K_h=0\cdot22$, $0\cdot30$, and $1\cdot0$ g-mol l^{-1} the results as calculated for these values of K_h are plotted in Figures 2, 3, and 4. A comparison of the results for $K_h=0\cdot13$ and $0\cdot22$ g-mol l^{-1} (Figs. 1 and 2) shows that the fitting of the experimental results to the expected quadratic function is relatively insensitive to the value of K_h. For a value of $K_h=1\cdot0$ g-mol l^{-1} (Fig. 4), there is a wide scatter of experimental points. A value of $K_h=0\cdot30$ g-mol l^{-1} (Fig. 3) gives a better agreement between the experimental results and the expected quadratic relation ; and the conclusion is reached that this is the value of the

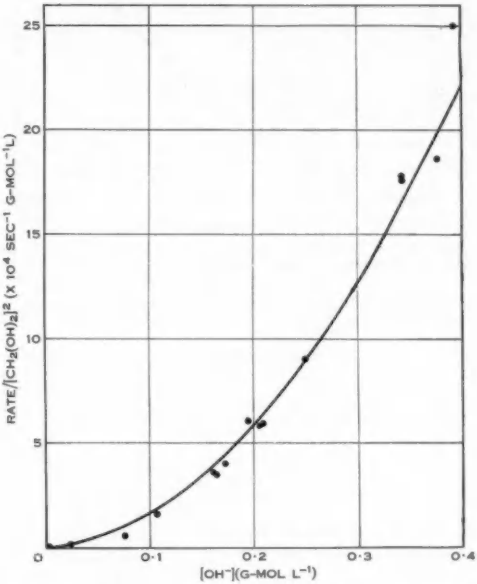


Fig. 2.—Graph of rate/$[CH_2(OH)_2]^2$ against $[OH^-]$ for $K_h=0\cdot22$.

hydrolysis constant needed by the kinetic data if they are to fit a general rate equation based on a plausible reaction mechanism. For a hydrolysis constant of $K_h=0\cdot30$ g-mol l^{-1}

$k_0=0\cdot0$,

$k_1=3\cdot35\times10^{-4}$ sec^{-1} g-mol^{-2} l^2, and

$k_2=9\cdot02\times10^{-3}$ sec^{-1} g-mol^{-3} l^3.

The Cannizzaro reaction of formaldehyde can therefore be described as the sum of a third and fourth order reaction, if corrections are made for the amount of methylene glycol anion present.

It has been mentioned in a previous paper (Martin 1954), that the measurement of the dissociation constant of methylene glycol by the electrometric method is not entirely satisfactory, and it is therefore assuring that a value of the same

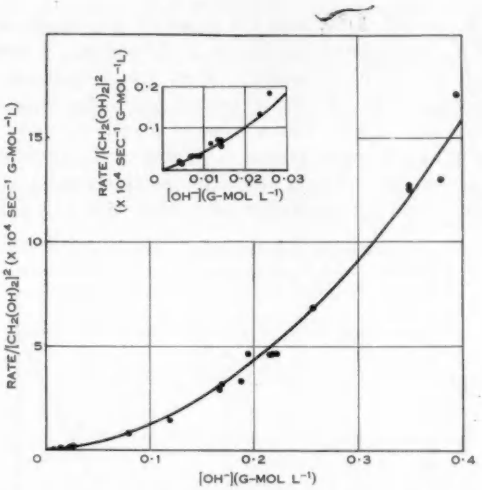


Fig. 3.—Graph of rate/$[CH_2(OH)_2]^2$ against $[OH^-]$ for $K_h = 0{\cdot}30$.

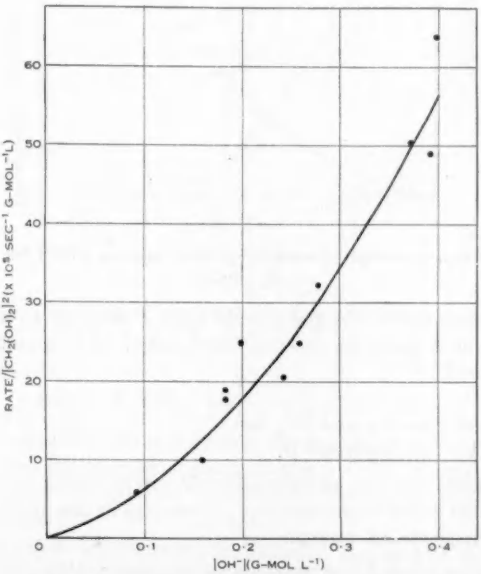


Fig. 4.—Graph of rate/$[CH_2(OH)_2]^2$ against $[OH^-]$ for $K_h = 1{\cdot}0$.

magnitude should be obtained from the kinetic experiments. At 40 °C the hydrolysis constants of 0·13 and 0·30 g-mol l^{-1} correspond to pK values of 12·7 and 13·1 respectively.

The value of k_2 is approximately 27 times greater than k_1, and k_0 is negligible. This relation of k_2, k_1, and k_0 can be explained either by a low concentration of $^+CH_2OH$, or by the small reactivity of $CH_2(O^-)(OH)$ and by the much greater reactivity of $CH_2(O^-)_2$.

It is surprising that $k_0=0$, because it means that there is no reaction between

$$^+CH_2OH \text{ and } CH_2(O^-)(OH).$$

Wadano, Trogus, and Hess (1934) have obtained a value of 20 for the determination of the pK value of the ionization $CH_2(OH)_2 \rightleftharpoons {}^+CH_2OH + OH^-$. For the alkali and formaldehyde concentrations used in this investigation, the concentration of $^+CH_2OH$ is of the order 10^{-19} g-mol l^{-1} or smaller, and therefore it can be assumed that the concentration of $^+CH_2OH$ is too small for it to take a detectable part in the reaction.

Since k_1 represents the velocity constant for the sum of the two reactions,

$$^+CH_2OH \text{ with } CH_2(O^-)_2,$$

and,

$$CH_2{=}O \text{ with } CH_2(O^-)(OH),$$

it is not possible from the kinetic evidence to distinguish between them. Again it can be argued that the concentration of $^+CH_2OH$ is too small for the reaction between

$$^+CH_2OH \text{ and } CH_2(O^-)_2$$

to occur. Therefore k_1 is the velocity constant for the reaction between

$$CH_2{=}O \text{ and } CH_2(O^-)(OH).$$

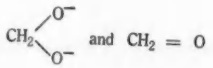
The experimental evidence therefore agrees with the mechanism suggested by Ingold (1953), that it is a simultaneous reaction between $CH_2{=}O$ and the hydride ion donors

$$CH_2(O^-)(OH) \text{ and } CH_2(O^-)_2.$$

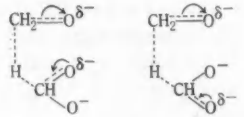
The alternative mechanism, involving an initial hemiformal formation, offers no interpretation of a fourth order reaction.

Since k_2 is greater than k_1, and the concentration of is very small compared with , the reactivity of is therefore greater than

If the transition states for both reactions are compared, the transition state for the reaction between



exhibits a resonance, which would lower the activation energy and cause an increase in rate. The strong inductive effect of the two $-O^-$ groups would greatly assist the release of a hydride ion:



It is now possible to understand why other workers only obtained a third order reaction for the Cannizzaro reaction of formaldehyde. For instance, Pajunen (1950) varied the alkali concentration from 0·025 to 0·10N with a corresponding variation in the formaldehyde concentration, so as to maintain a 2 : 1 ratio of formaldehyde to alkali. He found a very small change in the third order constants, which are given in Table 3 at 60 °C.

TABLE 3

THIRD ORDER VELOCITY CONSTANTS FOR THE CANNIZZARO REACTION

NaOH (g-mol l^{-1})	CH_2O (g-mol l^{-1})	Calc. k_3 at 40 °C ($\times 10^{-1}$ sec^{-1} g-$mol^{-2}l^2$)	$k_{3obs.}$ at 60 °C ($\times 10^{-3}$ sec^{-1} g-$mol^{-2}l^2$)
0·1	0·2	4·02	1·57
0·06	0·12	4·14	1·63
0·04	0·08	4·11	1·71
0·025	0·05	4·00	1·75
0·05	0·05	4·82	1·80

If the third and fourth order velocity constants k_1 and k_2, which have been derived from the experimental data for a hydrolysis constant $K_h = 0{\cdot}30$ g-mol l^{-1}, are used to calculate the rate according to equation (5), then the third order constants k_3 may be calculated from rate $= k_3ab^2$, assuming there is only a third order reaction. This has been done at 40 °C, using concentrations of formaldehyde and alkali identical with those used by Pajunen at 60 °C, and it will be noticed from Table 3 that there is almost no variation in the calculated third order constant. Therefore, the period of half-life will correspond to a third

order reaction as was shown by Pajunen. Pajunen also doubled the alkali concentration at a constant formaldehyde concentration, and an examination of Table 3 shows that this also produces no great change in the third order velocity constant.

This discussion indicates that in order to establish definitely the relationship between the concentrations of the different reactants and the rate, it is necessary to alter the concentration of reactants relative to one another over a wide range.

Pfeil (1951) showed the reaction was first order with respect to alkali at low alkali concentrations, and second order with respect to formaldehyde at high alkali concentrations. According to the conclusions reached in the present paper, the reaction would be expected to be limiting third and fourth order respectively at these extreme alkali concentrations, and would be second order with respect to formaldehyde throughout the whole range of alkali concentrations. But the order with respect to alkali would change gradually from first to second as the alkali concentration increased, and therefore in order to use the method adopted by Pfeil (1951), it is necessary to determine the order with respect to both reactants at the extreme concentrations.

Pfeil (1951) showed that the catalytic activities of the bases of Tl, Ca, Ba, Li, Na, K, and $N(CH_3)_4$ were in the inverse order to their basic strength. To explain this, Pfeil propounded a mechanism in which the cation formed a complex with two formaldehyde molecules, and then within this complex, a hydride ion moved from one carbon atom to the other. If such a mechanism operated, the addition of salts of these cations should markedly alter the rate. This was found to be the case for Ba and Tl, but the addition of Na_2SO_4 had no effect on the rate. Apparently some such mechanism applies for Ba and Tl, in addition to the third and fourth order reaction discussed here, but not for Na or K.

It would be very useful if a rate equation could be derived involving a, b, k_1, k_2, y, and t, but if it was derived it would be an extremely complex function. Therefore the most convenient way to express the results is to quote the third order velocity constant, together with the NaOH and formaldehyde concentrations for which it was derived as in Table 2.

III. Experimental

Carbonate-free NaOH was prepared by filtering 50 per cent. NaOH rapidly through a sintered glass funnel, and diluting with CO_2-free water. The NaOH solution was adjusted to 1·0N and stored in "Polythene" or wax-coated bottles.

The formaldehyde solution was prepared by heating paraformaldehyde under reflux with water until it had passed into solution, and the solution was filtered, analysed, and diluted to 1·0N.

For the kinetic runs, aliquots of NaOH, CH_2O, and when required, the amount of 1·00N KNO_3 needed to maintain the ionic strength of the final solution at $\mu=0·4$ were diluted to 100 ml with CO_2-free water. Aliquots (7·55 ml) of this solution were placed in constricted "Monax" tubes, sealed

under argon, and placed in the thermostat. After allowing 10 min for the tubes and the thermostat to reach the required temperature, the initial tubes were removed from the thermostat and the time measured from this instant. The reaction was stopped by immersing the tubes in a freezing mixture of equal volumes of carbon tetrachloride and chloroform mixed with crushed solid carbon dioxide. For analysis each tube was crushed under water in a thick-walled glass vessel.

The thermostat was maintained constant to within 0·02 °C.

The initial NaOH concentration was determined by titration with dilute H_2SO_4, using bromocresol purple as indicator.

The formaldehyde was determined by a modified Romijn's cyanide method (Walker 1953, p. 388), in which strongly acidified $AgNO_3$ solution containing 4 ml concentrated HNO_3 to every g $AgNO_3$, was added to the almost neutralized reaction product between formaldehyde and cyanide. The solution was filtered and excess $AgNO_3$ titrated potentiometrically with ammonium thiocyanate. The amount of alkali originally present and the amount formed from the cyanohydrin reaction was approximately known, and an amount of H_2SO_4 equivalent to this was added to neutralize the CH_2O-KCN reaction mixture. A high acidity was essential because the AgCN must be precipitated in acid solution to avoid large discrepancies. In Romijn's original method the CH_2O-KCN reaction mixture was added to the acid $AgNO_3$. The procedure was altered in order to reduce the number of operations by allowing precipitation of the whole sample in the vessel in which the tube was crushed.

The third order velocity constants were calculated from the formula:

$$k_3=\frac{2}{t(2a-b)}\left\{\frac{1}{b-y}-\frac{1}{b}-\frac{2\cdot303}{2a-b}\log_{10}\frac{b(a-y/2)}{a(b-y)}\right\},$$

which is derived from

$$\frac{dy}{dt}=k_3\left(a-\frac{y}{2}\right)(b-y)^2,$$

where a and b are the initial alkali and formaldehyde concentrations respectively, and y is the change in formaldehyde concentration at time t. Since a third order law holds within a run, the rate is given by k_3ab^2, where k_3 is the third order constant calculated for those particular concentrations of a and b.

For those runs in which the alkali or formaldehyde concentrations are low, that is, runs No. 1–11 and 24–26, the change in formaldehyde concentration y was related to t by the empirical relationship

$$y=\frac{t}{m+nt},$$

where m and n are coefficients which were evaluated from the linear relation

$$\frac{t}{y}=m+nt,$$

by the method of least squares. The rate at any particular time t was obtained by differentiation and is given by

$$\frac{dy}{dt} = \frac{m}{(m+nt)^2}.$$

IV. Acknowledgments

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THE CHEMICAL CONSTITUENTS OF AUSTRALIAN *FLINDERSIA* SPECIES

VI. THE STRUCTURE AND CHEMISTRY OF FLINDERSINE

By R. F. C. Brown,* J. J. Hobbs,* G. K. Hughes,* and E. Ritchie*

[*Manuscript received July* 1, 1954]

Summary

The alkaloid, flindersine, is shown to be 2′,2′-dimethyl-α-pyrano(5′,6′-3,4)-2-quinolone and some aspects of its chemistry are discussed. The constitutions of some derivatives of 4-hydroxy-2-quinolone are clarified and the synthesis of dictamnic acid is described. The synthesis confirms the structure previously suggested for dictamnine.

I. Introduction

Flindersia australis R.Br. is a large tree reaching a height of 130 ft and a diameter of 4 ft, which is found in rain-forests from north of the Richmond River in New South Wales to central southern Queensland. The timber which is known commercially as native teak and Crow's ash is yellowish brown, hard, heavy, and oily. It possesses a distinctive odour, is not attacked by borers, white ants, or other insects, and is used in shipbuilding.

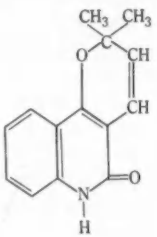
In 1914, in the first recorded work on any of the *Flindersia* species, Matthes and Schreiber reported the isolation from the wood in 2 per cent. yield of a colourless alkaloid, m.p. 182–183 °C, with decomposition commencing at about 170 °C, which they named flindersine. On the basis of elementary analyses (Found: C, 61·9; H, 5·7; N, 6·1 per cent.) and a cryoscopic molecular weight determination in benzene (Found: 446·1) they assigned to it the formula $C_{23}H_{26}O_7N_2$ (Calculated: C, 62·4; H, 5·9; N, 6·3 per cent.; mol. wt. 442·2). They described its picrate, lemon yellow needles, m.p. 174 °C, after sintering at 170 °C (not analysed) and its dibromide, a white crystalline powder, which began to darken at 160 °C, sintered at 170 °C, and melted at 180 °C (Found: Br, 27·93 per cent. Calc. for $C_{23}H_{26}O_7N_2Br_2$: Br, 26·6 per cent.). Flindersine was found to have a weakly alkaline reaction, to be optically inactive, and to be insoluble in water, sparingly soluble in light petroleum, but soluble in chloroform, ethanol, benzene, glacial acetic acid, hydrochloric acid, sulphuric acid, caustic alkali, glycerol, paraffin, and fatty oils. From its solubility in alkali it was concluded that one or more phenolic groups were present. It did not reduce Fehling's solution either as such or after treatment with hydrochloric acid, showing that it was not a glycoside. Neither pyridine nor quinoline could be detected with certainty in the products of zinc dust distillation. Positive

* Department of Organic Chemistry, University of Sydney.

tests were given with the usual alkaloid reagents but the substance had no toxic properties.

A new examination of the wood has now yielded a colourless substance, m.p. 185–186 °C (decomp.), which analyses and molecular weight determinations show must be $C_{14}H_{13}O_2N$. The discrepancy between this result and Matthes and Schreiber's was largely removed when it was found that they had miscalculated their carbon and hydrogen results. Recalculation gave C, 75·5 and H, 5·9 per cent. in better agreement with C, 70·4 and H, 5·7 per cent. calculated for $C_{14}H_{13}O_2N$. Their bromine analysis on the bromo-derivative (27·93 per cent.) is also in fair agreement with Br, 26·1 per cent. calculated for $C_{14}H_{12}O_2NBr$. Although there are other discrepancies there can be no doubt that the two substances are identical and the name, " flindersine ", is therefore retained.

It is shown below that flindersine has the structure I. Before this was established the evidence obtained was difficult to reconcile with any structure. Of those at all possible, II appeared to require the least number of assumptions



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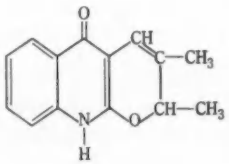


(II)

and until it was recognized that three important pieces of evidence were misleading it was believed to be substantially correct. The confusion was due to (i) an unexpected molecular rearrangement, (ii) a reaction between a critical degradation product and the solvent used to recrystallize it, and (iii) misleading analytical results. How these factors appeared to favour structure II will be pointed out briefly below.

II. Properties of Flindersine

Flindersine, a colourless optically inactive substance, contained no methoxyl group. One active hydrogen was present and terminal methyl group estimations gave values ranging from 0·82 to 1·02, indicating the presence of one or possibly two such groups. With ethanolic gallic acid and concentrated sulphuric acid, or with gallic acid and slightly diluted sulphuric acid, a positive Labat methylenedioxy test was given but under the usual conditions in the absence of ethanol or water a reddish purple colour was obtained. Also since the test was not given under any conditions by bromoflindersine or dihydroflindersine (see below) it was concluded that a methylenedioxy-group was absent. Positive tests were given with the usual alkaloid reagents and an orange colour with ferric chloride. The alkaloid readily yielded a picrate, m.p. 178 °C.

It decolourized bromine in chloroform without evolution of hydrogen bromide and since several recrystallizations were required before pure bromoflindersine, $C_{14}H_{12}O_2NBr$, m.p. 218 °C, was obtained, the latter was evidently formed by addition of bromine to a double bond followed by gradual elimination of hydrogen bromide during recrystallization. The presence of one double bond was also shown by the formation of dihydroflindersine only, even on prolonged catalytic hydrogenation. Flindersine could not be acetylated with acetic anhydride in the presence of anhydrous sodium acetate at 100 °C nor did it react with diazomethane. It was unaffected by heating with methyl iodide in a sealed tube at 100 °C, but with methyl iodide and potassium carbonate in acetone it yielded *N*-methylflindersine, $C_{15}H_{15}O_2N$, showing the presence of an imino-group.

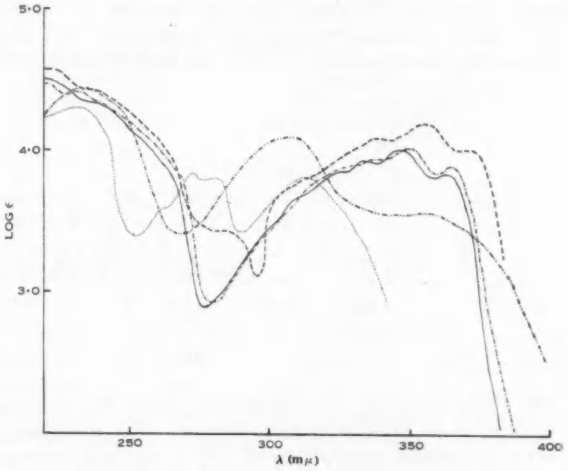


Fig. 1.—Ultraviolet spectra.
—— Flindersine.
···· Dihydroflindersine.
–·–· *N*-Methylflindersine.
---- Bromoflindersine.
–··– 4-Hydroxy-2-quinolone-3-carboxaldehyde.

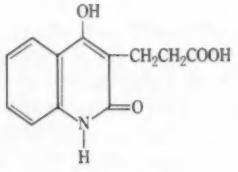
Flindersine behaved as a very weak base. It was soluble in concentrated hydrochloric acid but was precipitated unchanged by the addition of an equal volume of water, and was not extracted from chloroform solution by 10 per cent. hydrochloric acid. These properties suggested that either an amide or vinylogous amide system was present. It may be stated here that boiling with 15 per cent. sulphuric acid yielded a dimer, m.p. 355–357 °C. The alkaloid was insoluble in cold dilute sodium hydroxide but dissolved slowly on boiling. However, acidification precipitated only reddish brown amorphous material. After flindersine had been subjected to slow prolonged distillation with 30 per cent. potassium hydroxide, 4-hydroxy-2-quinolone was isolated from the residue,

and the distillate contained a mixture of carbonyl compounds, but several attempts to separate them (as their 2,4-dinitrophenylhydrazones) were unsuccessful. Further evidence that a quinoline nucleus was present in the alkaloid was obtained by a zinc dust distillation which gave quinoline. Although both of these latter reactions involved very vigorous conditions, the results were thought to be significant since the other known alkaloids of *Flindersia* species are all quinoline derivatives (Anet *et al.* 1952; Cannon *et al.* 1952*b*; Brown *et al.* 1954).

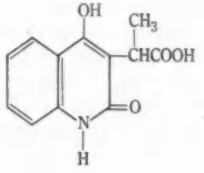
In Figure 1 are shown the ultraviolet absorption curves for flindersine, bromoflindersine, dihydroflindersine, *N*-methylflindersine, and 4-hydroxy-2-quinolone-3-carboxaldehyde (Asahina and Inubuse 1932). The very close similarity of the curves for the alkaloid and its methyl derivative shows that no major structural change has been effected by methylation. On the other hand the broad band of the flindersine curve with its maxima at 334, 347, and 364 mμ has been replaced in the curve for dihydroflindersine by two peaks of lower intensity at shorter wavelengths (271, 313 mμ). This suggests that in flindersine a double bond is conjugated with the quinoline nucleus and support for this hypothesis is obtained from the curve for 4-hydroxy-2-quinolone-3-carboxaldehyde. In the case of bromoflindersine, as expected, the maxima have shifted to longer wavelengths and the intensity has increased.

III. Permanganate Oxidation of Flindersine

Flindersine was readily oxidized by potassium permanganate in acetone. When the crude solid acidic product was boiled with ethanol a soluble substance $C_{12}H_{11}O_4N$ was readily separated from a very sparingly soluble substance $C_{10}H_7O_4N$. Both of these were soluble in aqueous sodium bicarbonate and gave reddish brown ferric tests. The latter was hydrolysed by boiling with either aqueous sodium hydroxide or hydrochloric acid to carbon dioxide and 4-hydroxy-2-quinolone. Since the nitrogen is present in an imino-group and a carbon-carbon double bond is attached to the 3-position of the quinoline nucleus in flindersine it follows that the acid must be 4-hydroxy-2-quinolone-3-carboxylic acid.



(III)



(IV)

The other substance, which also behaved as an acid, gave a methyl derivative by brief treatment with diazomethane. At its melting point, 208 °C, it evolved carbon dioxide but the residue was uncrystallizable. The possibility that it was either 3-(2′-carboxyethyl)-4-hydroxy-2-quinolone (III) or 3-(1′-carboxyethyl)-4-hydroxy-2-quinolone (IV) was considered. Both substances were

synthesized by reactions described later (Section VIII) but were found to be different, having different melting points and giving negative ferric tests. In the course of this comparison it was noted that the ultraviolet absorption curve of the C_{12} acid was markedly dissimilar to that of IV but similar to that of the C_{10} acid (Fig. 2). This together with the similar ferric tests given by each substance suggested that in the C_{12} acid also the carboxyl group was attached directly to the 3-position of the quinoline nucleus. Confirmation of this was obtained by

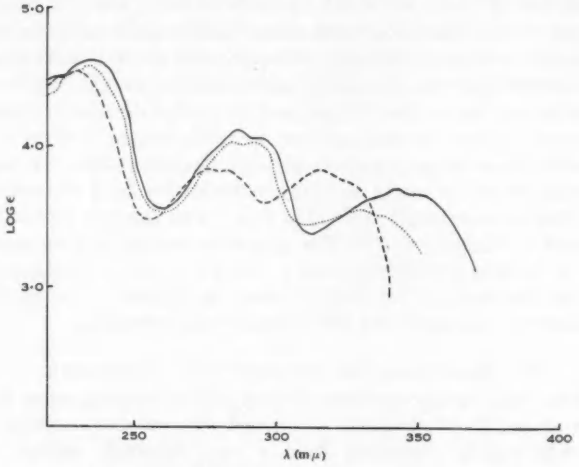
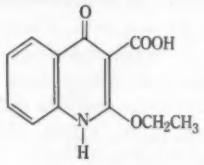


Fig. 2.—Ultraviolet spectra.
—— Acid, $C_{12}H_{11}O_4N$.
···· Acid, $C_{10}H_7O_4N$.
---- 3-(1′-Carboxethyl)-4-hydroxy-2-quinolone.

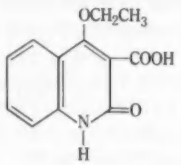
hydrolysing the C_{12} acid with either acid or alkali when carbon dioxide and 4-hydroxy-2-quinolone were formed. The other product of the hydrolysis was ethanol, which was proved by a positive iodoform reaction on the distillate from the acid or alkaline hydrolysis and by the isolation of *S*-ethyl*iso*thiuronium picrate after heating the acid with hydriodic acid and adding thiourea and picric acid to the distillate. Also the acid contained one ethoxyl group and one terminal methyl group. The C_{12} acid must therefore be either V, VI, or even possibly VII. It was shown to be identical with the substance prepared by reduction of diethyl *o*-nitrobenzoylmalonate by the method of Bischoff (1889) followed by hydrolysis by the method of Asahina, Ohta, and Inubuse (1930) to which structure V was assigned. (See, however, Section VIII, where it is proved to be VII.)

The production of V and the results of the terminal methyl group estimations provided some support for structure II for the alkaloid, but it was difficult to account for the formation of the C_{10} acid unless it was postulated that it was formed by hydrolysis of the ethoxyl group under the mild alkaline conditions of the oxidation. However, all attempts to effect such a hydrolysis were

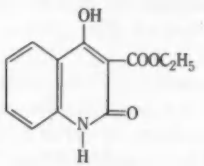
fruitless nor could the C_{12} be oxidized to the C_{10} acid by permanganate in acetone, or in water, or by sodium dichromate in acetic acid, under a variety of conditions. In most experiments it was readily attacked but no crystalline substances could be isolated.



(V)

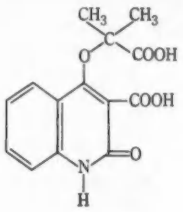


(VI)



(VII)

Eventually it was discovered that neither the C_{10} nor the C_{12} acid was a true primary oxidation product of flindersine. When the crude solid product of the oxidation of flindersine was recrystallized from acetone instead of ethanol it was found to be a single substance. This acid, which will be referred to as flindersinic acid, analysed for $C_{14}H_{13}O_6N$. When heated it evolved carbon dioxide and acidic vapours but the residue was amorphous. Hydrolysis with dilute acid proceeded more smoothly yielding carbon dioxide and 4-hydroxy-2-quinolone together with α-hydroxy*iso*butyric acid, identified by analysis and comparison with an authentic specimen. It follows that flindersinic acid is VIII or IX and that flindersine is I or X.



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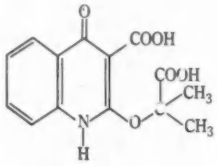
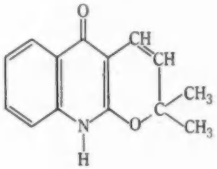


(IX)

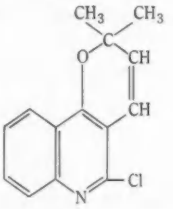


(X)

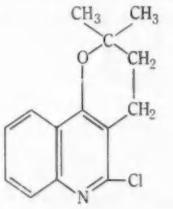
The formation of the C_{10} and the C_{12} acids was then examined. When pure flindersinic acid was boiled with absolute ethanol, or methanol containing a trace of phosphoric acid, it gave the C_{12} acid or the corresponding methoxy-derivative respectively, but when moist, freshly precipitated flindersinic acid, still containing traces of the phosphoric acid used to precipitate it, was boiled with 95 per cent. ethanol both the C_{10} and the C_{12} acids were formed. It was also found, surprisingly enough, that boiling the C_{10} acid with ethanol and a trace of phosphoric acid produced the C_{12} acid. This result meant that it could not be assumed that flindersinic acid was directly converted by alcoholysis to the C_{12} acid (then believed to be V) and that flindersinic acid was necessarily IX. The decision between the linear and angular structures for flindersine was reached through the degradation of chlorodeoxy-derivatives of the alkaloid.

IV. Chlorodeoxyflindersine and Its Degradation

By the action of phosphorus oxychloride flindersine gave chlorodeoxyflindersine, $C_{14}H_{12}ONCl$ (XI). It was hoped to remove the chlorine from this substance by catalytic hydrogenation and then oxidize the product to a quinolone-3-carboxylic acid but the chlorine was unexpectedly inert. With hydrogen and



(XI)



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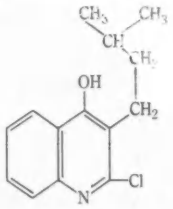

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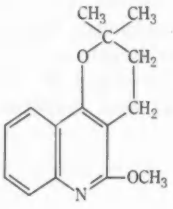
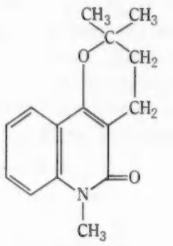
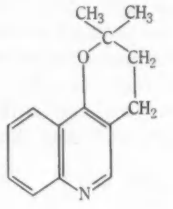


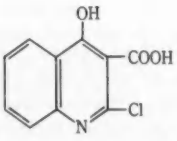
(XIV)



(XV)



(XVI)



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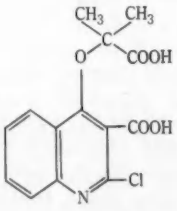
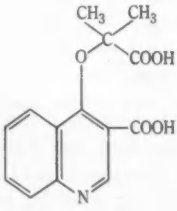


(XVIII)

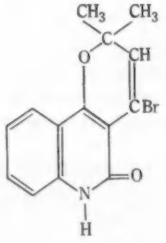


(XIX)

Raney nickel or platinum there was produced a mixture of chlorodeoxydihydroflindersine, $C_{14}H_{14}ONCl$ (XII) and a substance $C_{14}H_{16}ONCl$ (XIII) apparently formed by hydrogenolysis of the pyran ring. In the former substance the chlorine was still relatively inert. It was unaffected by sodium methoxide in boiling methanol but in boiling xylene it gave *O*-methyldihydroflindersine (XIV) which like other 2- or 4-methoxyquinolines (Asahina, Ohta, and Inubuse 1930)

was isomerized by heating with methyl iodide at 100 °C to *N*-methyldihydroflindersine (XV). The halogen of XII was not removed by further catalytic hydrogenation or by lithium aluminium hydride, but sodium amalgam yielded deoxydihydroflindersine, $C_{14}H_{15}ON$ (XVI). Unfortunately this substance was not suitable for further degradation since not only was it stable to oxidizing agents but also was recovered largely unchanged after boiling with hydriodic acid and phosphorus.

Oxidation of chlorodeoxyflindersine with permanganate in acetone, however, readily afforded a less soluble acid $C_{10}H_6O_3NCl$ (XVII) in small yield and a more soluble acid $C_{14}H_{12}O_5NCl$, chlorodeoxyflindersinic acid (XVIII) in moderate yield. The acid XVII gave a reddish brown ferric test and decomposed at its melting point, 196 °C, evolving carbon dioxide but the residue could not be purified. Hydrolysis with boiling dilute hydrochloric acid produced 4-hydroxy-2-quinolone. Chlorodeoxyflindersinic acid gave a reddish brown ferric test also and formed a dimethyl ester with diazomethane. Its structure was analogous to that of flindersinic acid since although alkaline hydrolysis gave dark intractable material, acid hydrolysis yielded carbon dioxide, 4-hydroxy-2-quinolone and α-hydroxy*iso*butyric acid. On hydrogenation in dry methanol in the presence of palladium chloride and anhydrous potassium acetate it gave an acid $C_{14}H_{13}O_5N$ which was smoothly pyrolysed to 4-hydroxyquinoline-3-carboxylic acid, identified by comparison with an authentic specimen (Cannon *et al.* 1952*a*) and by decarboxylation to 4-hydroxyquinoline. The acid $C_{14}H_{13}O_5N$ therefore was XIX and it followed that the chlorine was originally at the 2-position of the quinoline ring. Hence chlorodeoxyflindersinic acid was XVIII, chlorodeoxyflindersine was XI, and flindersine had the angular structure I. The other substances described above had the structures shown.



(XX)

Although there are no close analogies, a consideration of the inductive and resonance effects suggests that bromoflindersine has structure XX and that in flindersine dimer the residues are joined through the 3- and 4-positions of the pyran rings with the double bond being retained in the latter residue.

V. *N*-Methylflindersine and Its Derivatives

Flindersine dissolved in methanol was not affected by ethereal diazomethane even after 30 hours. Dimethyl sulphate and aqueous alcoholic alkali produced a red viscous oil from which nothing crystalline could be separated and a similar

result was obtained when dimethyl sulphate and potassium carbonate in dry acetone was used. However, prolonged refluxing with a large excess of methyl iodide and anhydrous potassium carbonate in dry acetone gave a good yield of *N*-methylflindersine (XXI). No colour was obtained with ferric chloride but like flindersine it was unstable to hot aqueous alkali and gave an anomalous Labat methylenedioxy test. Catalytic hydrogenation yielded *N*-methyldihydroflindersine (XV) identical with the substance obtained above. This unreactive substance was only slowly attacked by boiling hydriodic acid and phosphorus giving amorphous products.

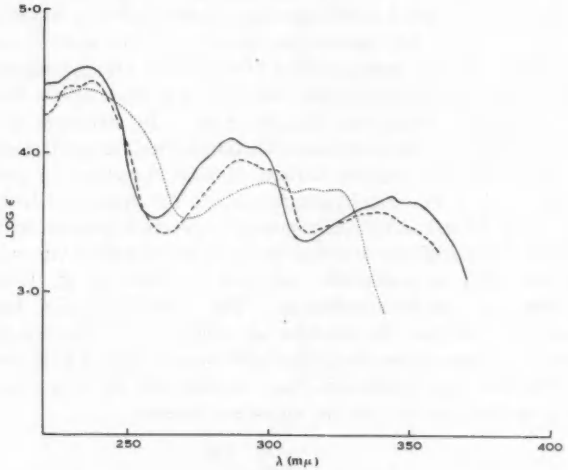
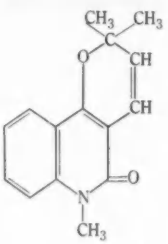


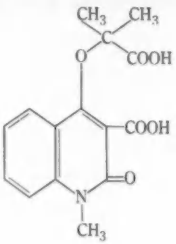
Fig. 3.—Ultraviolet spectra.
—— Acid, $C_{12}H_{11}O_4N$.
---- *N*-Methylflindersinic acid.
···· Chlorodeoxyflindersinic acid.

By oxidation of XXI with permanganate in acetone, *N*-methylanthranilic acid and *N*-methylflindersinic acid, $C_{15}H_{15}O_6N$ (XXII), were formed. The analytical values originally obtained for this substance and its dimethyl ester indicated its formula to be $C_{13}H_{13}O_5N$ and the close relationship of this to $C_{12}H_{11}O_4N$, the acid initially isolated from the oxidation of flindersine, caused some confusion which was not decreased by the observation that its ultraviolet absorption spectrum was very similar to that of the C_{12} acid (Fig. 3, where the curve for chlorodeoxyflindersinic acid is given also). Unlike flindersinic acid, XXII when crude did not readily react with methanol or ethanol but in other respects the two acids were similar. It gave a deep red ferric test and formed a dimethyl ester. On pyrolysis carbon dioxide was evolved leaving a residue of amorphous material and 4-hydroxy-1-methyl-2-quinolone. The acid was stable to alkali but hydrolysis with acid yielded 4-hydroxy-1-methyl-2-quinolone and α-hydroxy*iso*butyric acid.

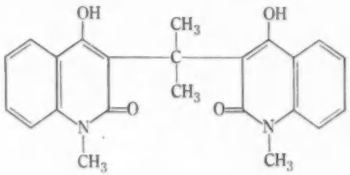
The 4-hydroxy-1-methyl-2-quinolone required for comparison was prepared from 4-chloro-2-quinolone by the method of Friedländer and Müller (1887). In an attempt to find a simpler synthesis the dipotassium derivative of 4-hydroxy-2-quinolone was refluxed with methyl iodide in acetone but the product, obtained in small yield, analysed for $C_{23}H_{22}O_4N_2$. The substance also obtained by refluxing 4-hydroxy-2-quinolone, methyl iodide, and potassium carbonate in dry acetone, probably had the structure XXIII.



(XXI)



(XXII)



(XXIII)

VI. Dihydroflindersine

Flindersine was not reduced at room temperature and pressure by hydrogen in the presence of 10 per cent. palladium-charcoal, but when platinum or Raney nickel was used, dihydroflindersine was readily obtained, reduction stopping at this stage. The same substance was produced by hydrogenation of bromoflindersine in the presence of platinum and by reduction of flindersine with Raney alloy and alcoholic alkali at room temperature or at 90 °C, although at the higher temperature the alkali brought about some decomposition of the alkaloid. In agreement with the structures assigned, the ultraviolet absorption spectrum of dihydroflindersine differs considerably from that of flindersine but closely resembles those of 4-hydroxy-1-methyl-2-quinolone and 4-methoxy-2-quinolone (Fig. 4). In this connection the spectrum of deoxydihydroflindersine (XVI) is of some interest.

Dihydroflindersine was a very stable substance. It was unaffected by boiling acetic anhydride in the presence of sodium acetate, by boiling alcoholic potassium hydroxide, by permanganate in acetone, by ethereal diazomethane, and even by fusion with potassium hydroxide at 300 °C, and by boiling with hydriodic acid and phosphorus for 60 hours. Indeed the latter reagent could be used to prepare it from flindersine. However, when heated with hydriodic acid at 210 °C in a sealed tube it was converted to 4-hydroxy-2-quinolone. Alkylation with methyl iodide and potassium carbonate in acetone gave *N*-methyldihydroflindersine (XV) and treatment with phosphorus oxychloride yielded chlorodeoxydihydroflindersine (XII).

VII. Flindersine Glycols and Related Substances

The slow addition of chromic anhydride to flindersine in acetic acid at 40 °C oxidized it to the substances $C_{16}H_{17}O_5N$ (XXIV) and $C_{16}H_{15}O_5N$ (XXV). The

former contained one acetyl group but attempts to hydrolyse it by aqueous alkali gave only amorphous products. However with sodium methoxide in dry methanol at room temperature it was smoothly converted to $C_{14}H_{15}O_4N$ which was evidently the *trans*-glycol XXVI. When this, or XXIV, was boiled with dilute acid a ketone $C_{14}H_{13}O_3N$, was obtained by a pinacol-pinacolone rearrangement and was characterized by its 2,4-dinitrophenylhydrazone and its *p*-nitrobenzylidene derivative, $C_{21}H_{16}O_5N_2$. The ketone was assigned the structure XXVII from a consideration of its ultraviolet absorption spectrum. By

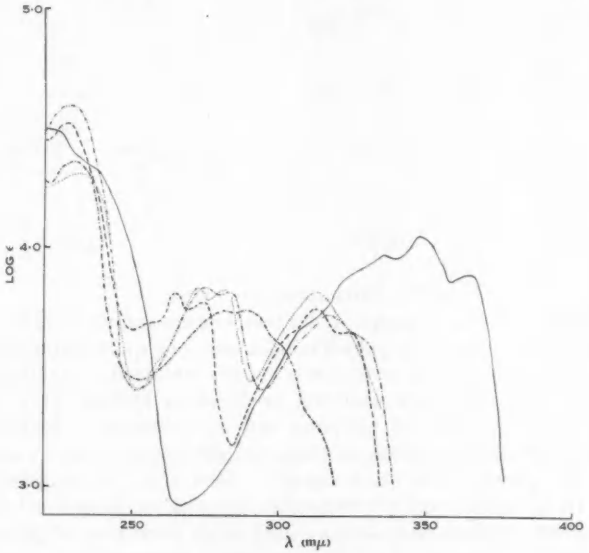


Fig. 4.—Ultraviolet spectra.
—— Flindersine.
···· Dihydroflindersine.
–·–· 4-Hydroxy-1-methyl-2-quinolone.
···· 4-Methoxy-2-quinolone.
–·–· Deoxydihydroflindersine.

comparison with the curve for 4-hydroxy-2-quinolone-3-carboxaldehyde (Fig. 5) it was clear that the carbonyl group was not conjugated with the quinoline nucleus.

The second product of the oxidation also contained one acetyl group which treatment with hot dilute acid or alkali or sodium methoxide in methanol removed, yielding the ketol $C_{14}H_{13}O_4N$. Catalytic hydrogenation of this using a platinum catalyst gave a mixture from which a little of the *trans*-glycol could be separated but attempts to effect the reverse change by oxidation with chromic anhydride in pyridine gave either unchanged starting material or amorphous products. The spectra of the ketol and its acetate (Fig. 5) showed that in each

the carbonyl group was conjugated with the aromatic system and they therefore had the structures XXVIII and XXV respectively. Also, since the ketol acetate was probably derived from the glycol monoacetate, the latter was probably XXIV.

When *N*-methylflindersine was oxidized under the same conditions only one product, $C_{17}H_{19}O_5N$ (XXIX) was isolated. Removal of the acetyl group by sodium methoxide in methanol yielded the *trans*-glycol XXX which hot dilute acid then converted to the ketone XXXI.

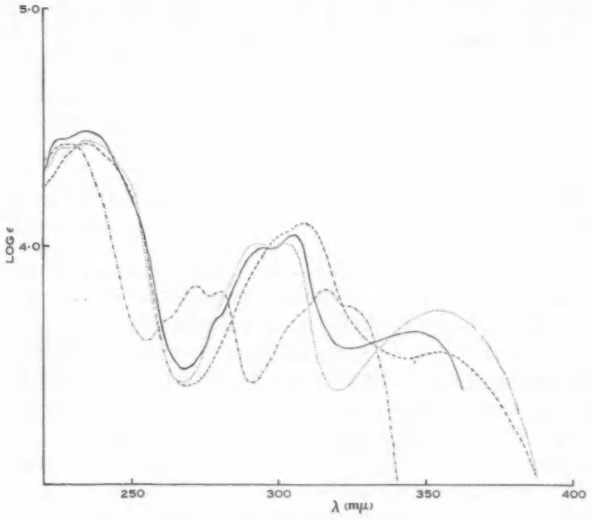
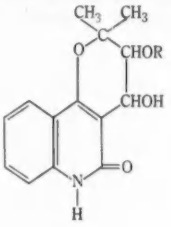


Fig. 5.—Ultraviolet spectra.
—— Ketol $C_{14}H_{13}O_4N$.
···· Ketoacetate $C_{16}H_{15}O_5N$.
–·–· Ketone $C_{14}H_{13}O_3N$.
---- 4-Hydroxy-2-quinolone-3-carboxaldehyde.

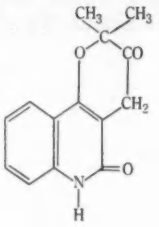
Treatment of flindersine in benzene with osmium tetroxide in the presence of pyridine afforded the *cis*-glycol XXXII which hot dilute acid rearranged to the same ketone XXVII obtained from the *trans*-glycol. The *cis*-glycol was rapidly attacked by lead tetra-acetate but the oxidation was anomalous. The major product was 4-hydroxy-2-quinolone-3-carboxaldehyde and the other a substance, m.p. 178 °C (decomp.). On recrystallization from either ethyl acetate, methanol, acetone, or chloroform it separated in a solvated form from which in spite of many attempts, solvent could not be completely removed without decomposition. The analytical figures for the best specimen were far from being in satisfactory agreement with the values calculated for the expected formula $C_{14}H_{13}O_4N$, and the nature of the substance remains obscure. Oxidation of the *trans*-glycol gave the same products but the reaction was much slower.

The ketol XXVIII reacted even more slowly and after 1 week much unchanged starting material was recovered, the other product being 4-hydroxy-2-quinolone-3-carboxylic acid.

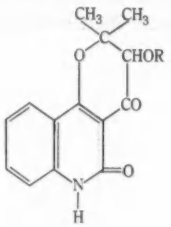
After the substance, m.p. 178 °C, was hydrolysed by boiling with 10 per cent. hydrochloric acid, 4-hydroxy-2-quinolone-3-carboxaldehyde was obtained on cooling. Addition of excess phenylhydrazine to the buffered filtrate and



(XXIV) R=$COCH_3$
(XXVI) R=H

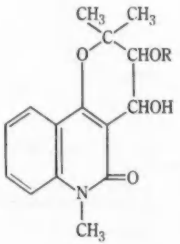


(XXVII)

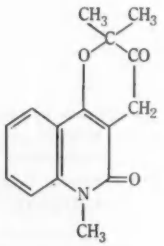


(XXV) R=$COCH_3$
(XXVIII) R=H

refluxing then gave diacetyl phenylosazone. The formation of this substance from the other product of the hydrolysis, presumably acetoin, was observed fairly early in the degradation of flindersine and was interpreted as evidence for structure II. It was only later when confirmatory evidence for the presence of acetoin was sought that the identity of the primary hydrolysis product was recognized.



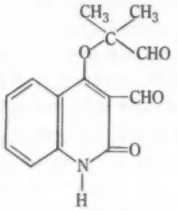
(XXIX) R=$COCH_3$
(XXX) R=H



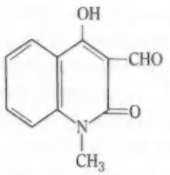
(XXXI)

Since the lead tetra-acetate oxidation of the *cis*-glycol was abnormal, its oxidation by periodate was examined. This reaction, which was complete in 20 minutes at room temperature, gave only one product, a substance, m.p. 126 °C, of the expected formula $C_{14}H_{13}O_4N$ (XXXIII). When this was hydrolysed and the products treated in the same way as the substance from the lead tetra-acetate oxidation, 4-hydroxy-2-quinolone-3-carboxaldehyde and diacetyl phenylosazone were again obtained. However, it was observed that if the hydrolysis was effected under milder conditions and the filtrate from the

4-hydroxy-2-quinolone-3-carboxaldehyde further oxidized with periodate, then the product was not acetaldehyde, which would be expected from acetoin, but was acetone. It was also found that if the filtrate was subjected to steam distillation the distillate contained α-hydroxy*iso*butyraldehyde which was isolated and identified as its 2,4-dinitrophenylhydrazone (Braude and Timmons 1953). It was clear then that the initially formed α-hydroxy*iso*butyraldehyde, which would certainly yield acetone by periodate oxidation, had rearranged under the acid conditions to acetoin and indeed this rearrangement had already been reported in the literature (Danilow and Venus-Danilowa 1934). It also followed that the substance, m.p. 126 °C, had the expected structure XXXIII.



(XXXIII)



(XXXIV)

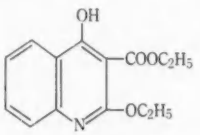
By oxidation with osmium tetroxide the *cis*-glycols were also obtained from chlorodeoxyflindersine and *N*-methylflindersine. The latter glycol on acid treatment rearranged to the same ketone XXXI as the *trans*-glycol. Oxidation with lead tetra-acetate in this case too was abnormal since the only isolable product was 4-hydroxy-1-methyl-2-quinolone-3-carboxaldehyde (XXXIV) which was identified by comparison with an authentic specimen synthesized by a Reimer-Tiemann reaction on 4-hydroxy-1-methyl-2-quinolone. This aldehyde was also obtained by ozonolysis of *N*-methylflindersine. Ozonolysis of chlorodeoxyflindersine or flindersine on the other hand gave only amorphous products.

VIII. The Structures of Dictamnine and Some Derivatives of 4-Hydroxy-2-quinolone

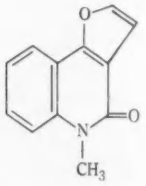
Two reactions have been used to synthesize derivatives of 4-hydroxy-2-quinolone-3-carboxylic acid. Bischoff (1889) prepared diethyl *o*-nitrobenzoylmalonate and reduced it in absolute ethanol with zinc and dry hydrogen chloride. From the complex mixture produced he isolated a substance, m.p. 107 °C, " in not very satisfactory yield " which was soluble in dilute sodium carbonate to a pale reddish solution and gave a deep violet-red ferric test. On the basis of a concordant analysis for carbon and hydrogen he assigned to it the constitution, ethyl 2-ethoxy-4-hydroxyquinoline-3-carboxylate (XXXV) but did not prepare the related acid or any other derivative. By reducing the nitro-compound with zinc and acetic acid he obtained in small yield an acid which he isolated as its silver salt. This acid was thought to be 4-hydroxy-2-quinolone-3-carboxylic acid but no evidence apart from analyses for carbon, hydrogen, and silver was presented, nor was the acid itself described. When the reduction

was effected with tin and aqueous alcoholic hydrochloric acid 4-hydroxy-2-quinolone was obtained in good yield and its identity established. He also isolated a small amount of a substance, m.p. 228 °C, giving a negative ferric test, to which the constitution, 2-ethoxy-4-hydroxyquinoline was assigned solely from an analysis for carbon and hydrogen.

The first method of reduction was later used by Asahina, Ohta, and Inubuse (1930) in an attempt to establish the structure of dictamnic acid which would have been 4-methoxy-2-quinolone-3-carboxylic acid if dictamnine had a linear structure, but 2-methoxy-4-hydroxyquinoline-3-carboxylic acid if it had an angular structure. They reduced dimethyl *o*-nitrobenzoylmalonate with zinc and dry hydrogen chloride in " absolute alcohol " and obtained a crude product which they stated was 2-methoxy-4-hydroxyquinoline-3-carboxylic acid ester. It may be noted here that an *ethyl* ester would be expected by *trans*-esterification unless methanol was used as the solvent. The product was allowed to stand overnight with 5 per cent. methanolic potash and the solution then acidified. An acid, m.p. 225 °C, giving a deep violet-red ferric test, was obtained in small yield. It was analysed for nitrogen only and was assigned the structure, 2-methoxy-4-hydroxyquinoline-3-carboxylic acid. Since it was not identical with dictamnic acid it was concluded that the latter was 4-methoxy-2-quinolone-3-carboxylic acid and that dictamnine had a linear structure. Evidence supporting this was obtained later when Asahina and Inubuse (1932) synthesized pseudodictamnine which would be expected to be XXXVI and found it to be different from *iso*dictamnine.



(XXXV)



(XXXVI)

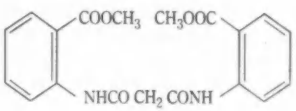
Anet *et al.* (1952) hydrolysed with 5 per cent. methanolic potassium hydroxide the product from the reduction of dimethyl 6-nitroveratroylmalonate in dry methanol with zinc and dry hydrogen chloride and obtained a substance, m.p. 330 °C, giving a reddish brown ferric test and described as 4-hydroxy-2,6,7-trimethoxyquinoline-3-carboxylic acid. It was not identical with kokusaginic acid and hence kokusaginine was assigned a linear structure.

The other reaction was discovered by Koller (1927) who heated methyl-anthranilate and diethylmalonate with sodium ethoxide in absolute ethanol at 150 °C. The sodio-derivative on acidification gave a product, m.p. 203–204 °C, with a yellowish brown ferric test. He concluded that it was methyl 4-hydroxy-2-quinolone-3-carboxylate and emphasized that it was not the expected ethyl ester. He stated that alkaline hydrolysis yielded methanol, carbon dioxide, and 4-hydroxy-2-quinolone. The latter was satisfactorily identified but no

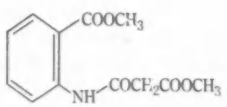
evidence was adduced for the formation of methanol. The ester was analysed for carbon, hydrogen, nitrogen, and methoxyl. The results for carbon and nitrogen were good, for hydrogen poor, and for methoxyl irrelevant since they agree equally well for an ethoxyl group.

Lutz *et al.* (1946) applied a modification of the reaction to methyl 4-chloroanthranilate. The half-amide was obtained by heating this amine with diethyl malonate in the first step, and in the second was cyclized by sodium ethoxide in absolute ethanol. The product, without purification or analysis, was hydrolysed and decarboxylated to 7-chloro-4-hydroxy-2-quinolone without isolating any intermediates.

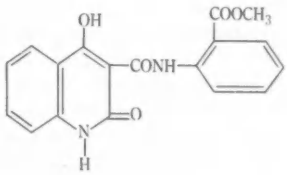
Both syntheses have now been re-examined. When methyl anthranilate is heated with dimethyl malonate either the diamide XXXVII or the monoamide XXXVIII is obtained according to the conditions. Cyclization of the former with sodium methoxide in dry methanol gives a substance $C_{18}H_{14}O_5N_2$, which must have structure XXXIX. Cyclization of the monoamide by the same reagent gives a substance $C_{11}H_9O_4N$, m.p. 224–225 °C, containing one methoxyl group, but cyclization by sodium ethoxide in dry ethanol gives a substance $C_{12}H_{11}O_4N$, m.p. 208 °C, containing one ethoxyl group. It follows that these are the methyl (XL) and ethyl (VII) esters respectively of 4-hydroxy-2-quinolone-



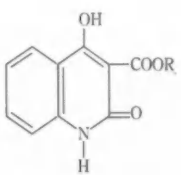
(XXXVII)



(XXXVIII)



(XXXIX)

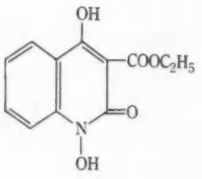


(XL) R=CH_3
(VII) R=C_2H_5

3-carboxylic acid. Both substances are soluble in aqueous sodium bicarbonate and both give reddish brown ferric tests. The substance, m.p. 208 °C, is identical with the substance, m.p. 208 °C, prepared by the ethanolysis of flindersinic acid and with the substance, m.p. 208 °C, obtained by esterifying 4-hydroxy-2-quinolone-3-carboxylic acid with ethanol. In addition, Koller's substance, m.p. 203–204 °C, as expected, must be a slightly impure form of this substance. Also, the substance, m.p. 224–225 °C, is identical with the substance, m.p. 224 °C, formed by methanolysis of flindersinic acid.

The reduction of dimethyl *o*-nitrobenzoylmalonate with zinc and dry hydrogen chloride was repeated using methanol. The crude product when treated with 5 per cent. methanolic potassium hydroxide gave in low yield a substance $C_{11}H_9O_4N$, m.p. 225 °C, which was undoubtedly identical with the product obtained by Asahina, Ohta, and Inubuse (1930). However, it was soluble in aqueous sodium bicarbonate, gave a reddish brown ferric test, and was identical with the methyl ester (XL). It follows that their conclusions regarding the structures of dictamnic acid and dictamnine were not necessarily valid. However, it is shown below that they were, indeed, correct.

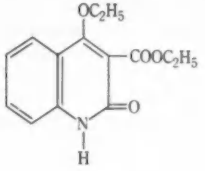
Further experiments were carried out on the reduction of the more readily available diethyl ester. This proved to be a rather capricious reaction. The product was always complex, the yields low and not always duplicable. Reduction in dry ethanol followed by alkaline hydrolysis of the crude intermediate gave in low yield a substance $C_{12}H_{11}O_4N$, m.p. 208 °C, which was identical with the ethyl ester VII. However, it was also found that this substance could be isolated directly from the crude intermediate by fractional crystallization, without alkaline hydrolysis. Under certain conditions two other substances could also be separated from the crude intermediate. One of these, $C_{12}H_{11}O_5N$, m.p. 165 °C, contained one ethoxyl group, was sparingly soluble in dilute sodium bicarbonate but soluble in dilute sodium carbonate, and gave a deep violet ferric test. It was probably the cyclic hydroxamic acid (XLI), since it could not be hydrolysed with acid to 4-hydroxy-2-quinolone. A similar substance was obtained by Heller and Wunderlich (1914) by reducing *o*-nitrobenzylidenemalonic acid with zinc and acetic acid (see also Culvenor 1953). The constitution of the other product $C_{14}H_{15}O_4N$, m.p. 103 °C, which is undoubtedly identical with Bischoff's substance, m.p. 107 °C, is discussed later.



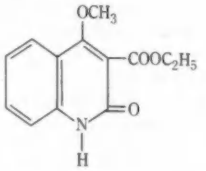
(XLI)

Attempts to convert 4-hydroxy-2-quinolone-3-carboxylic acid to its methyl ester (XL) by diazomethane were unsuccessful. This was probably due to the very slight solubility of the acid and the consequent prolonged exposure of the presumably first formed methyl ester to diazomethane (cf. behaviour of VII in Section IX (*ww*)). Equally fruitless were attempts to hydrolyse either of the esters XL or VII to the acid. Either they were recovered unchanged or were converted directly to 4-hydroxy-2-quinolone. The ethyl ester VII with diazoethane gave a substance $C_{14}H_{15}O_4N$, m.p. 173–174 °C, containing two ethoxyl groups, which was insoluble in sodium bicarbonate solution and gave a negative ferric test. It was formulated as ethyl 4-ethoxy-2-quinolone-3-carboxylate

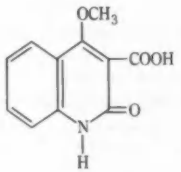
(XLII) since Arndt, Ergener, and Kutlu (1953) have shown that 4-hydroxy-2-quinolone with diazomethane gave 4-methoxy-2-quinolone and none of the isomeric 4-hydroxy-2-methoxyquinoline. On the same grounds the product $C_{13}H_{13}O_4N$, m.p. 145 °C, which was obtained by the action of diazomethane on the ethyl ester VII and which behaved like XLII, was assigned structure XLIII. It was hydrolysed by acid to 4-hydroxy-2-quinolone, but with alkali an acid $C_{11}H_9O_4N$, m.p. 260 °C, was obtained. This acid was identical with an authentic specimen of dictamnic acid and moreover methyl dictamnate prepared by the action of diazomethane on dictamnic acid was identical with the substance obtained from the ester XL by the same reagent. Hence dictamnic acid is XLIV and dictamnine has a linear structure. Attempts to decarboxylate dictamnic acid were unsuccessful.



(XLII)



(XLIII)



(XLIV)

The structure of Bischoff's substance is now considered. It contained two ethoxyl groups, was insoluble in dilute sodium bicarbonate but soluble in aqueous sodium carbonate to a colourless solution, gave a reddish brown ferric test, and was not identical with XLII. It could not be prepared from the ester VII by treatment with dry hydrogen chloride in dry ethanol with or without zinc chloride, and was recovered unchanged after standing overnight at room temperature with 5 per cent. ethanolic potassium hydroxide. These experiments showed that it was not a precursor of VII. However, hydrolysis of the substance with acid gave 4-hydroxy-2-quinolone and hydrolysis with aqueous alkali at 90 °C gave an acid, m.p. 164 °C. This acid which could not be obtained analytically pure, was decarboxylated to a phenol $C_{11}H_{11}O_2N$, m.p. 175 °C, containing one ethoxyl group and giving an orange-red ferric test. Diazoethane converted it to 2,4-diethoxyquinoline. Hence the phenol was 2-ethoxy-4-hydroxyquinoline and the substance, m.p. 228 °C, with a negative ferric test, to which Bischoff assigned this structure must have some other constitution. It also followed that the substance, m.p. 103 °C, was ethyl 2-ethoxy-4-hydroxyquinoline-3-carboxylate (XXXV), as Bischoff stated, although its formation by the reduction of diethyl *o*-nitrobenzoylmalonate was difficult to accept.

Further work on other furoquinoline alkaloids on these lines is in progress.

The two acids III and IV (Section III) were prepared by reacting *o*-nitrobenzoyl chloride with the appropriately substituted malonic esters and reducing the products with phosphorus and hydriodic acid according to the method of Gabriel (1918). The same reactions were used to synthesize 4-hydroxy-3-(2′-methylbutyl)-2-quinolone which was prepared as a possible degradation product of flindersine.

IX. Experimental

Melting points are uncorrected. Light petroleum refers to the fraction of b.p. 60–90 °C. Ultraviolet absorption spectra were measured in ethanol on a Beckman DU ultraviolet spectrophotometer. Analyses are by Dr. K. W. Zimmermann, C.S.I.R.O., Melbourne, and by Miss B. Stevenson and the late Mrs. E. Bielski, University of Sydney.

(*a*) *Isolation of Flindersine.*—The dried milled wood was exhausted with light petroleum either by cold percolation or in a continuous extractor. On concentrating the extract and cooling, a crystalline solid separated. It was purified by recrystallization from ethanol, ethyl acetate, and methanol, being finally obtained as flat colourless needles, m.p. 185–186 °C (decomp.), $[\alpha]_D^{20}$ 0° (*c*, 1·0 in ethanol) (Found: C, 74·0; H, 5·8; N, 6·3; OCH_3, nil; $(C)CH_3$, 5·4, 6·8, 6·1; active H, 0·6%; mol. wt. (by cryoscopy in benzene), 205, 224. Calc. for $C_{14}H_{13}O_2N$: C, 74·0; H, 5·8; N, 6·2; $1\times(C)CH_3$, 6·6; $1\times$active H, 0·4%; mol. wt., 227). The original extract also contained a yellow oil but nothing crystalline could be separated from it although some flindersine was probably present. The best yield (0·35%) was obtained from seasoned wood, fresh wood giving only very small amounts of flindersine. In this case the larger amounts of yellow oil presumably prevented the crystallization of the flindersine. A similar explanation probably accounts for the very low yields obtained even from seasoned wood when methanol was the solvent used.

Flindersine could not be isolated from the bark, nor could hesperedin.

The picrate crystallized from ethanol in long yellow needles, m.p. 178 °C (Found: N, 12·2%. Calc. for $C_{20}H_{16}O_9N_4$: N, 12·3%).

(*b*) *Bromoflindersine.*—To a solution of flindersine (0·5 g) in chloroform (10 ml) a 3% solution of bromine in chloroform was added at room temperature until decolourization no longer occurred. The solid, m.p. 180–182 °C, obtained by evaporating the solution was recrystallized several times from ethanol, yielding colourless needles, m.p. 218 °C (decomp.) (Found: C, 54·9; H, 4·0; N, 4·7; Br, 26·1%. Calc. for $C_{14}H_{12}O_2NBr$: C, 54·9; H, 4·0; N, 4·6; Br, 26·1%).

(*c*) *Flindersine Dimer.*—Flindersine (0·3 g) was heated under reflux with sulphuric acid (15%; 10 ml) for 2 hr. After cooling and diluting, the *product* was collected, washed, and recrystallized from acetic acid as small colourless needles, m.p. 355–357 °C (decomp.) (Found: C, 73·5; H, 5·9; N, 6·0%. Calc. for $C_{28}H_{26}O_4N_2$: C, 74·0; H, 5·8; N, 6·2%).

(*d*) *Degradation of Flindersine by Alkali.*—A mixture of flindersine (1 g) and potassium hydroxide (30%; 50 ml) was slowly distilled for 10 hr, and the distillate collected in a saturated solution of 2,4-dinitrophenylhydrazine in sulphuric acid (10%). The volume of liquid in the flask was maintained by the addition of water and heating was regulated so that about 10 ml passed over each hour. The crude dinitrophenylhydrazones (*c.* 0·5 g) melted indefinitely at about 120 °C, but all attempts to isolate a pure substance by chromatography on alumina or by fractional crystallization were fruitless.

The residual solution in the flask was cooled in a freezing mixture. The crystalline material which separated was collected, dissolved in water, and the solution acidified. The precipitated product (0·3 g) crystallized from glacial acetic acid as colourless needles, m.p. and mixed m.p. with an authentic specimen of 4-hydroxy-2-quinolone, 354 °C (Found: C, 67·4; H, 4·7%. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·4%). The acetyl derivative prepared by heating the substance (0·1 g) with acetic anhydride (2 ml) and pyridine (2 drops) on the water-bath for 1 hr and then diluting with ice water, crystallized from ethanol as colourless needles, m.p. and mixed m.p. with an authentic specimen (Ashley, Perkin, and Robinson 1930) 214 °C (Found: C, 65·1; H, 4·5%. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5%). The nitroso-derivative, prepared by gradual acidification of an ice-cold solution of the substance and sodium nitrite in dilute sodium hydroxide, crystallized from glacial acetic acid in red needles, m.p. and mixed m.p. with an authentic specimen 202 °C (decomp.).

Because of its high m.p. these two derivatives were also used on other occasions to identify 4-hydroxy-2-quinolone.

(*e*) *Zinc Dust Distillation.*—An intimate mixture of flindersine (0·2 g) and zinc dust (10 g) was placed in a combustion tube and a layer of zinc dust (10 g) poured on top of it. A stream

of hydrogen was passed through the tube whilst it was heated, first at the zinc layer and then at the mixture. The product was collected in a liquid air trap. The brown oil from five such distillations was extracted with light petroleum and the solution passed through a short column of alumina. Only the fraction eluted by light petroleum was soluble in 3% hydrochloric acid and the others were discarded. The acid solution was washed with ether, then basified and extracted with ether. The ethereal solution was extracted with 1% hydrochloric acid and the soluble bases again returned to ether by basification. The oil thus obtained was dissolved in warm ethanolic picric acid. On cooling, a picrate was obtained which after many recrystallizations from ethanol finally gave yellow needles, m.p. 201–202 °C, undepressed by admixture with quinoline picrate. Insufficient material was obtained for analysis.

(*f*) *Permanganate Oxidation of Flindersine.*—Powdered potassium permanganate (3·9 g) was added during 4 hr to a stirred solution of flindersine (2 g) in acetone (200 ml) at room temperature. When reaction appeared to have ceased, the manganese dioxide was collected, washed with acetone, and extracted with cold 2% sodium hydroxide. Acidification of the extracts with phosphoric acid precipitated a pale yellow solid (1·4 g).

(i) Recrystallization of the crude dried acid from a large volume of acetone gave slightly yellow needles of *flindersinic acid* (VIII) (Found: C, 57·8; H, 4·5; N, 4·5%. Calc. for $C_{14}H_{13}O_6N$: C, 57·7; H, 4·5; N, 4·8%). When heated the acid evolved acidic vapours, presumably of methylacrylic acid, at c. 180 °C without melting or darkening and then melted with evolution of carbon dioxide at 320–325 °C, leaving an uncrystallizable residue (cf. behaviour of 4-hydroxy-2-quinolone-3-carboxylic acid described below). The acid (0·25 g) suspended in ether (100 ml) was shaken at 0–5 °C with ethereal diazomethane (from 2 g *N*-nitrosomethylurea) until it dissolved (c. 30 min). Excess reagent was destroyed by acetic acid and the solution washed with dilute sodium carbonate and water. The residue obtained by removing the solvent crystallized in contact with ethyl acetate. The *dimethyl ester* crystallized from methanol in colourless needles, m.p. 192 °C (Found: C, 60·2; H, 5·4; N, 4·5; OCH_3, 19·0%. Calc. for $C_{16}H_{17}O_6N$: C, 60·2; H, 5·4; N, 4·4; $2\times OCH_3$, 19·4%).

Flindersinic acid (0·4 g) was heated under reflux with hydrochloric acid (3N; 10 ml) for 2 hr. The precipitate which separated on cooling was collected and recrystallized from glacial acetic acid giving colourless needles (0·15 g) of 4-hydroxy-2-quinolone, m.p. 354 °C, further identified as above. The acid filtrate was saturated with sodium chloride, filtered, and extracted continuously with ether. Evaporation of the ether left a crystalline solid which on sublimation at 100 °C (bath temp.)/1 mm gave colourless needles. Recrystallization from light petroleum afforded long colourless hygroscopic needles of α-hydroxy*iso*butyric acid (0·05 g), m.p. and mixed m.p. with an authentic specimen, 76 °C (Found: C, 45·7; H, 8·0%. Calc. for $C_4H_8O_3$: C, 46·2; H, 7·8%).

(ii) When the crude *moist* acid (dry wt. 1·3 g) was boiled with ethanol (95%; 75 ml) only part of it dissolved. The insoluble fraction was filtered from the hot solution and recrystallized from glacial acetic acid giving colourless needles (0·4 g) of *4-hydroxy-2-quinolone-3-carboxylic acid* (Found: C, 58·6; H, 3·5; N, 6·9%. Calc. for $C_{10}H_7O_4N$: C, 58·5; H, 3·4; N, 6·8%). It melted at 324 °C with evolution of carbon dioxide but the residue was uncrystallizable. It was soluble in aqueous sodium bicarbonate and gave a reddish brown ferric test. When it (0·5 g) was refluxed with hydrochloric acid (10%; 60 ml) for 1 hr carbon dioxide was evolved and 4-hydroxy-2-quinolone (0·3 g), m.p. and mixed m.p. 354 °C after recrystallization from glacial acetic acid, was obtained. The same products were obtained by hydrolysis with 20% potassium hydroxide for 1 hr.

The ethanol solution obtained above on concentration gave a product which after repeated recrystallization from ethanol afforded colourless needles (0·45 g) of *ethyl 4-hydroxy-2-quinolone-3-carboxylate*, m.p. 208 °C (decomp., evolution of carbon dioxide), undepressed by admixture with the substance prepared by either of the synthetic methods described below (Found: C, 61·8; H, 4·8; N, 6·0; OC_2H_5, 19·5; (C)CH_3, 6·3%. Calc. for $C_{12}H_{11}O_4N$: C, 61·8; H, 4·8; N, 6·0; $1\times OC_2H_5$, 19·3; $1\times$(C)CH_3, 6·4%). It was soluble in aqueous sodium bicarbonate and gave a reddish brown ferric test. On heating with hydriodic acid, ethyl iodide was evolved and was identified by the preparation in the usual manner of *S*-ethyl*iso*thiuronium picrate, m.p.

and mixed m.p. 188 °C. When refluxed with sulphuric acid (10% ; 10 ml) for 1 hr the substance (0·25 g) gave carbon dioxide and 4-hydroxy-2-quinolone (0·1 g). By distilling the filtrate from the latter a distillate was obtained which readily gave a positive iodoform test. The same results were obtained by hydrolysis with 10% sodium hydroxide for 1·5 hr.

(*g*) *Alcoholysis of Flindersinic Acid.*—(i) Flindersinic acid (0·2 g) was refluxed with methanol (50 ml) containing a trace of syrupy phosphoric acid for 1 hr. The solution was evaporated to dryness and the yellow residue heated at 100 °C (bath temp.)/1 mm when α-hydroxy*iso*butyric acid sublimed. After recrystallization from light petroleum it had m.p. and mixed m.p. 76 °C. The non-volatile residue after several recrystallizations from a little methanol afforded colourless needles of *methyl 4-hydroxy-2-quinolone-3-carboxylate* (0·1 g), m.p. and mixed m.p. with the synthetic specimen prepared as below, 224 °C.

(ii) Ethanolysis of flindersinic acid was effected in exactly the same way and gave a product, m.p. and mixed m.p. 208 °C, after recrystallization from ethanol.

(*h*) *Esterification of 4-Hydroxy-2-quinolone-3-carboxylic Acid.*—The acid (0·3 g) was refluxed with ethanol (50 ml) containing a trace of syrupy phosphoric acid for 1 hr. The product (0·25 g) isolated by evaporating the reaction mixture had m.p. and mixed m.p. 208 °C, after recrystallization from ethanol.

(*i*) *Chlorodeoxyflindersine* (*XI*).—Flindersine (3 g) and freshly distilled phosphorus oxychloride (3 ml) were heated at 85 °C for 15 min and then refluxed for a further 15 min. After cooling, chloroform was added, the solution slowly poured into ice-cold ammonia, and the mixture shaken for 30 min. The organic layer was separated, washed, dried, and evaporated. The residue was dissolved in light petroleum and the solution passed through a short column of alumina. The combined filtrate and light petroleum eluates yielded a clear, nearly colourless oil (2·7 g) which did not crystallize even after regeneration from the *picrate* which separated from ethanol in yellow needles, m.p. 151 °C (Found : C, 50·9 ; H, 3·3 ; N, 11·9 ; Cl, 7·4%. Calc. for $C_{20}H_{15}O_9N_4Cl$: C, 50·6 ; H, 3·2 ; N, 11·8 ; Cl, 7·5%).

(*j*) *Hydrogenation of Chlorodeoxyflindersine.*—The chloro-compound (1·0 g) in ethanol (100 ml) was hydrogenated in the presence of Raney nickel (or platinum oxide) at room temperature and pressure for 6 hr when hydrogen uptake ceased. After filtering off the catalyst the filtrate was evaporated to a small bulk when *2-chloro-4-hydroxy-3-(3′-methylbutyl)quinoline* (XIII) (0·7 g) separated. It crystallized from ethanol-ethyl acetate in colourless prisms, m.p. 222 °C (Found : C, 67·4 ; H, 6·4 ; N, 5·5 ; Cl, 14·2%. Calc. for $C_{14}H_{16}ONCl$: C, 67·3 ; H, 6·5 ; N, 5·6 ; Cl, 14·2%).

From the original ethanol filtrate the more soluble *chlorodeoxydihydroflindersine* (XII) (0·1 g) was isolated. It crystallized from light petroleum in colourless needles, m.p. 55 °C (Found : C, 68·4 ; H, 5·7 ; Cl, 14·2%. Calc. for $C_{14}H_{14}ONCl$: C, 67·9 ; H, 5·7 ; Cl, 14·3%). The *picrate* formed stout yellow needles from ethanol, m.p. 173 °C (Found : C, 50·4 ; H, 3·4 ; Cl, 7·4%. Calc. for $C_{20}H_{17}O_9N_4Cl$: C, 50·4 ; H, 3·6 ; Cl, 7·5%).

(*k*) O-*Methyldihydroflindersine* (*XIV*).—A solution of chlorodeoxydihydroflindersine (0·45 g) in dry xylene (10 ml) was refluxed with dry, methanol-free sodium methoxide (from 0·06 g sodium) for 12 hr. After cooling, ether was added and the mixture washed with water. The solvents were removed by steam distillation and the residue extracted with ether. The ether was replaced with light petroleum and the solution passed through a column of alumina. Evaporation of the eluates gave an oil (0·3 g) which did not solidify. Its *picrate* crystallized from ethanol in yellow needles, m.p. 181 °C (Found : C, 53·4 ; H, 4·2 ; N, 11·7 ; OCH_3, 6·5%. Calc. for $C_{21}H_{20}O_9N_4$: C, 53·4 ; H, 4·3 ; N, 11·9 ; $1\times OCH_3$, 6·6%).

(*l*) N-*Methyldihydroflindersine* (*XV*).—A portion of the above oil (0·15 g) was heated with methyl iodide (5 ml) in a sealed tube at 100 °C for 6 hr. The brown residue left after removal of the excess reagent was dissolved in benzene and the solution chromatographed on alumina. The *substance* (0·05 g) obtained from the eluates crystallized from light petroleum in colourless needles, m.p. 138 °C, undepressed by admixture with a sample as prepared in (*q*) or (*x*) of Section IX.

(*m*) *Deoxydihydroflindersine* (*XVI*).—Carbon dioxide was passed through a boiling solution of chlorodeoxydihydroflindersine (0·2 g) in absolute ethanol (10 ml) whilst sodium amalgam (10%; 3 g) was added during 30 min. After heating for 30 min longer, the mixture was filtered and the filtrate evaporated under reduced pressure leaving a pale brown oil which did not solidify. The *picrate* crystallized from ethanol in yellow needles, m.p. 221 °C (Found: C, 54·2; H, 4·1; Cl<0·2%. Calc. for $C_{29}H_{18}O_8N_4$: C, 54·3; H, 4·1%).

(*n*) *Oxidation of Chlorodeoxyflindersine.*—Powdered potassium permanganate (5 g) was added gradually to a boiling solution of chlorodeoxyflindersine (2·3 g) in acetone (150 ml). When reaction had ceased, the manganese dioxide was collected, washed with acetone, and extracted with warm 2% sodium hydroxide. Acidification of the extracts gave a precipitate which was separated by crystallization from methanol into two substances. The less soluble substance, *2-chloro-4-hydroxyquinoline-3-carboxylic acid* (XVII) (0·1 g) (Found: C, 54·0; H, 2·7; Cl, 15·9%. Calc. for $C_{10}H_6O_3NCl$: C, 53·7; H, 2·7; Cl, 15·9%) formed colourless needles and gave a reddish brown ferric test. At its m.p. 196 °C, it evolved carbon dioxide but the residue could not be crystallized. Hydrolysis with boiling 10% hydrochloric acid in the usual way gave 4-hydroxy-2-quinolone.

The more soluble substance, *chlorodeoxyflindersinic acid* (XVIII) (0·9 g) (Found: C, 54·0; H, 3·7; N, 5·0, 4·2%. Calc. for $C_{14}H_{12}O_5NCl$: C, 54·3; H, 3·9; N, 4·5%. Note also calc. for $C_{12}H_{10}O_4NCl$: C, 53·8; H, 3·8; N, 5·2%) crystallized in colourless needles and gave a reddish brown ferric test. Its *dimethyl ester*, obtained by treating an ethereal solution of the acid with excess ethereal diazomethane for 6 min crystallized from light petroleum in pale cream prisms, m.p. 94 °C (Found: C, 57·1; H, 4·9; N, 4·2; Cl, 10·6; OCH_3, 18·0%. Calc. for $C_{16}H_{16}O_5NCl$: C, 56·9; H, 4·8; N, 4·2; Cl, 10·5; $2\times OCH_3$, 18·4%. Note also calc. for $C_{14}H_{14}O_5NCl$: C, 56·9; H, 4·8; N, 4·7; Cl, 12·0; $2\times OCH_3$, 20·9%). Hydrolysis of the acid with boiling 10% hydrochloric acid for 2 hr and working up as in Section IX (*f*) gave carbon dioxide, 4-hydroxy-2-quinolone, and α-hydroxy*iso*butyric acid.

(*o*) *Degradation of Chlorodeoxyflindersinic Acid.*—(i) The acid (0·4 g), anhydrous potassium acetate (0·4 g), palladium chloride (0·15 g), and dry methanol (50 ml) were shaken in an atmosphere of hydrogen at room temperature and pressure. After 5 hr the catalyst was filtered off, the filtrate evaporated almost to dryness, and water (30 ml) added. Acidification then gave the *acid* XIX (0·3 g) which crystallized from methanol in colourless needles, m.p. 266 °C (decomp. evolution of carbon dioxide) after sintering in the range 200–220 °C (Found: C, 61·0; H, 4·8%. Calc. for $C_{14}H_{13}O_5N$: C, 61·1; H, 4·8%). The m.p. was not depressed by admixture with 4-hydroxyquinoline-3-carboxylic acid.

(ii) The acid XIX (0·2 g) was heated in an oil-bath at 230 °C for 1 hr. A colourless acidic liquid, presumably methylacrylic acid, distilled from the solid leaving a powdery residue, which on recrystallization from methanol gave 4-hydroxyquinoline-3-carboxylic acid (0·1 g) as colourless needles, m.p. and mixed m.p. with an authentic specimen 266 °C (decomp. evolution of carbon dioxide) (Found: C, 63·4; H, 3·9; N, 7·1%. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%).

(iii) Decarboxylation was effected by heating the acid at 265–270 °C until frothing ceased. The residue on purification by sublimation *in vacuo* and recrystallization from ethanol-ether yielded colourless needles of 4-hydroxyquinoline, m.p. and mixed m.p. with an authentic specimen 199–200 °C.

(*p*) *N-Methylflindersine* (*XXI*).—Anhydrous potassium carbonate (5 g) was added to a solution of flindersine (2 g) in dry acetone (300 ml) and methyl iodide (15 ml) and the mixture refluxed for 4 hr. More ethyl iodide (5 ml) was then added and refluxing continued for a further 2 hr. After filtering, the acetone was removed and the residue taken up in chloroform. The washed and dried solution was evaporated and the residue extracted with light petroleum. By chromatography on alumina the *N-methylflindersine* (1·5 g) which appeared in the first eluates was separated from a little unchanged flindersine (0·15 g) and some dark material. It crystallized from light petroleum in colourless prisms, m.p. 84 °C (Found: C, 74·3; H, 6·3%; OCH_3, nil. Calc. for $C_{15}H_{13}O_2N$: C, 74·7; H, 6·3%).

(*q*) N-*Methyldihydroflindersine* (*XV*).—*N*-methylflindersine (0·25 g) in ethanol (25 ml) was hydrogenated in the presence of Raney nickel at room temperature and pressure. Hydrogen uptake ceased after 20 min. The product crystallized from light petroleum in colourless needles (0·21 g), m.p. 139 °C, and was identical with the substance prepared as in (*l*) or (*x*) of Section IX (Found: C, 74·1; H, 7·0; N, 5·9; NCH_3, 8·3%. Calc. for $C_{15}H_{17}O_2N$: C, 74·1; H, 7·0; N, 5·8; $1\times NCH_3$, 12·0%).

(*r*) *Oxidation of* N-*Methylflindersine*.—Oxidation of *N*-methylflindersine (2 g) in boiling acetone (300 ml) with potassium permanganate (4 g) was effected as usual. The manganese dioxide was extracted with warm dilute alkali and the extract acidified. The precipitate was collected and the filtrate after basification evaporated under reduced pressure to a small volume. Addition of acetic acid then gave crude *N*-methylanthranilic acid (0·15 g) which crystallized from ethanol as pale yellow needles, m.p. 177 °C alone or mixed with an authentic specimen (Found: C, 63·8; H, 6·2%. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0%).

The precipitate first obtained (1·2 g) on crystallization from methanol yielded N-*methylflindersinic acid* (XXII) as colourless needles, m.p. 161 °C (decomp.) (Found: C, 59·1, 58·8; H, 5·2, 5·0; N, 5·2, 4·7%. Calc. for $C_{15}H_{15}O_6N$: C, 59·0; H, 5·0; N, 4·6%. Note also calc. for $C_{13}H_{13}O_5N$: C, 59·3; H, 5·0; N, 5·3%). It gave a deep red ferric test and on brief treatment in ether with ethereal diazomethane a *dimethyl ester*, colourless prisms from ethyl acetate, m.p. 117 °C, was produced (Found: C, 61·9, 61·5; H, 5·9, 5·9; N, 4·6, 4·4; OCH_3, 18·2, 18·2%. Calc. for $C_{17}H_{19}O_6N$: C, 61·3; H, 5·8; N, 4·2; $2\times OCH_3$, 18·6%. Note also calc. for $C_{15}H_{17}O_5N$: C, 61·9; H, 5·9; N, 4·8; $2\times OCH_3$, 21·3%).

(*s*) *Pyrolysis of* N-*Methylflindersinic Acid*.—The acid (0·25 g) was heated in an atmosphere of nitrogen at about 20 mm pressure in an oil-bath at 160–180 °C. After decomposition was complete only carbon dioxide had collected in an attached liquid air trap. The residual solid consisted of some amorphous uncrystallizable material and 4-hydroxy-1-methyl-2-quinolone which crystallized from methanol as colourless plates (0·12 g), m.p. and mixed m.p. with an authentic specimen 264 °C (Found: C, 68·4; H, 5·0; N, 7·9%. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·2; N, 8·0%). Arndt, Ergener, and Kutlu (1953) give m.p. 272 °C. Further identification was provided by the preparation of an acetate, m.p. and mixed m.p. 149 °C, formed by heating the substance and acetic anhydride and pyridine at 100 °C for 1 hr, and a red nitroso-derivative, m.p. and mixed m.p. 189 °C (decomp.), obtained by acidifying a cold alkaline solution of the substance and sodium nitrite.

(*t*) *Hydrolysis of* N-*Methylflindersinic Acid*.—The acid (0·6 g) and hydrochloric acid (3N; 15 ml) were heated under reflux for 2 hr. The reaction mixture on working up as in Section IX (*f*) gave 4-hydroxy-1-methyl-2-quinolone (0·3 g) and α-hydroxy*iso*butyric acid (0·1 g).

(*u*) *Attempted Syntheses of 4-Hydroxy-1-methyl-2-quinolone*.—(i) To potassium hydroxide (1·4 g) in dry methanol (100 ml) was added 4-hydroxy-2-quinolone (2 g). After warming for a short time the solvent was removed under reduced pressure and dry acetone (100 ml) and methyl iodide (5 ml) added. The mixture was refluxed for 3 hr, then filtered and evaporated. The residue was extracted with chloroform, the extract washed, dried, and evaporated. The residue on crystallization from methanol afforded colourless needles (0·4 g) of a *substance*, probably XXIII, m.p. 252 °C (Found: C, 70·7; H, 5·6; N, 7·2%. Calc. for $C_{22}H_{22}O_4N_2$: C, 70·8; H, 5·7; N, 7·2%).

(ii) A mixture of 4-hydroxy-2-quinolone (0·5 g), anhydrous potassium carbonate (1 g), methyl iodide (1 ml), and dry acetone (50 ml) was refluxed for 8 hr, additional amounts of methyl iodide (2 ml) being added after 2 and 4 hr. The product (0·1 g) isolated as above had m.p. and mixed m.p. 252 °C.

(*v*) *Dihydroflindersine*.—(i) Flindersine (2·27 g) in ethanol (120 ml) was hydrogenated at room temperature and pressure in the presence of Raney nickel catalyst. The theoretical amount of hydrogen was absorbed in about 4 hr, uptake then ceasing. The *dihydro-derivative* (2·25 g) crystallized from ethyl acetate as colourless hexagonal plates, m.p. 229 °C (Found: C, 73·4; H, 6·6; N, 6·1%. Calc. for $C_{14}H_{15}O_2N$: C, 73·3; H, 6·6; N, 6·1%). A similar result was obtained when platinum was used.

(ii) Bromoflindersine (0·5 g) in glacial acetic acid (25 ml) hydrogenated under the same conditions with a platinum catalyst gave dihydroflindersine (0·3 g). No marked break in the rate of hydrogen uptake was observed.

(iii) Raney alloy (5 g) was added during 1·5 hr to a stirred solution of flindersine (0·5 g) in ethanol (30 ml) and potassium hydroxide (20%; 30 ml) at room temperature. Stirring was continued for a further 2 hr and the mixture then allowed to stand overnight. After filtering, ethanol was removed under reduced pressure, when crude dihydroflindersine (0·45 g), m.p. 224 °C, separated.

(iv) Raney alloy (5 g) was added during 2 hr to a boiling stirred solution of flindersine (0·5 g) in ethanol (20 ml) and potassium hydroxide (15%; 15 ml). After being left overnight, the mixture was worked up as above when a yellow gum was obtained. On standing in contact with ethyl acetate it yielded crude dihydroflindersine (0·3 g), m.p. 224 °C.

(v) Flindersine (0·4 g), red phosphorus (0·3 g), and concentrated hydriodic acid (6 ml) were refluxed for 2 hr. Water (20 ml) was added, the precipitate collected, and extracted with ethanol. Concentration and cooling then yielded dihydroflindersine (0·3 g), m.p. 227 °C.

(*w*) *Action of Hydriodic Acid on Dihydroflindersine.*—Dihydroflindersine (0·6 g) was heated with concentrated hydriodic acid (10 ml) in a sealed tube at 210 °C for 4 hr. The dark brown mixture was diluted and after being allowed to stand for some hours the liquid was decanted from the semi-solid product. After stirring with ethanol this was collected and recrystallized several times from glacial acetic acid giving finally 4-hydroxy-2-quinolone (0·15 g), m.p. 354 °C.

(*x*) *Alkylation of Dihydroflindersine.*—A mixture of dihydroflindersine (0·5 g), methyl iodide (5 ml), anhydrous potassium carbonate (10 g), and dry acetone (80 ml) was refluxed for 12 hr and then filtered. The acetone was distilled from the filtrate and the residue extracted with chloroform. The product isolated from the extract crystallized from light petroleum as colourless needles (0·44 g), m.p. 139 °C alone or mixed with substance prepared in (*l*) or (*q*) of Section IX.

(*y*) *Chlorodeoxydihydroflindersine.*—Dihydroflindersine (0·5 g) was treated with phosphorus oxychloride and the product isolated as in Section IX (*i*). It crystallized from light petroleum in colourless needles (0·4 g), m.p. and mixed m.p. with the substance prepared in Section IX (*j*) 55 °C.

(*z*) *Oxidation of Flindersine with Chromic Anhydride.*—A solution of chromic anhydride (1·8 g) in glacial acetic acid (30 ml) was added during 20 hr to a stirred solution of flindersine (5 g) in glacial acetic acid (70 ml) at 40 °C. After a further 2 hr at 40 °C the mixture was allowed to stand overnight, then diluted with water (500 ml), and shaken with chloroform (100 ml). The solid *A* which separated was filtered off and extraction with chloroform (2×100 ml then 6×50 ml) continued. On washing the combined extracts with water, aqueous sodium bicarbonate and water, and allowing to stand, more of *A* separated. Evaporation of the chloroform left a residue which by fractional crystallization from ethanol yielded a solid *B* and unchanged flindersine (0·3 g).

Recrystallization of *A* from methanol gave colourless needles (1·1 g), m.p. 219 °C, of *flindersine* trans-*glycol monoacetate* (XXIV) (Found: C, 63·3; H, 5·7; N, 4·8; CH_3CO, 13·9%. Calc. for $C_{16}H_{17}O_5N$: C, 63·4; H, 5·7; N, 4·6; $1 \times CH_3CO$, 14·1%). Recrystallization of *B* from ethyl acetate gave colourless needles (0·7 g) of the *ketol acetate* (XXV), m.p. 254 °C (Found: C, 63·6; H, 5·3; N, 4·9; CH_3CO, 13·4%. Calc. for $C_{16}H_{15}O_5N$: C, 63·8; H, 5·0; N, 4·7; $1 \times CH_3CO$, 14·1%).

(*aa*) *Flindersine* trans-*Glycol.*—Sodium (0·1 g) was dissolved in dry methanol (15 ml), the glycol monoacetate (0·25 g) added, and the mixture shaken at room temperature for 6 hr. The solution was neutralized with acetic acid and the solvent removed. Crystallization of the residue from aqueous methanol gave colourless needles (0·15 g), m.p. 243 °C, of the trans-*glycol* XXVI (Found: C, 64·4; H, 5·8; N, 5·6%. Calc. for $C_{14}H_{15}O_4N$: C, 64·4; H, 5·8; N, 5·4%).

(*bb*) *Rearrangement to the Ketone XXVII.*—The *trans*-glycol or its monoacetate (0·5 g) was heated under reflux with sulphuric acid (10%; 40 ml). The solid dissolved during 10 min but shortly afterwards the product began to separate. After 2 hr the mixture was cooled, diluted,

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and the product collected. The *ketone* XXVII (0·3 g) crystallized from ethanol in colourless needles, m.p. 239 °C (Found: C, 69·1; H, 5·4; N, 5·5%. Calc. for $C_{14}H_{13}O_3N$: C, 69·1; H, 5·4; N, 5·8%).

The *2,4-dinitrophenylhydrazone* crystallized from glacial acetic acid in orange needles, m.p. 251 °C (Found: C, 56·6; H, 4·3%. Calc. for $C_{20}H_{17}O_6N_5$: C, 56·7; H, 4·1%).

The p-*nitrobenzylidene derivative*, prepared by heating the ketone and *p*-nitrobenzaldehyde in benzene in the presence of a little piperidine for 8 hr, crystallized from glacial acetic acid in yellow needles, m.p. 305 °C (Found: C, 66·8; H, 4·3; N, 7·4%. Calc. for $C_{21}H_{16}O_5N_2$: C, 67·0; H, 4·3; N, 7·4%).

(*cc*) *Hydrolysis of the Ketol Acetate* (*XXV*).—(i) The acetate (0·4 g) was refluxed with sulphuric acid (10%; 40 ml) for 1·5 hr. After diluting, the product was collected and recrystallized from ethyl acetate. The *ketol* XXVIII (0·25 g) formed fine colourless needles, m.p. 221 °C (Found: C, 65·0; H, 5·2; N, 5·6%. Calc. for $C_{14}H_{13}O_4N$: C, 64·9; H, 5·1; N, 5·4%).

(ii) The acetate (0·5 g) was refluxed with sodium hydroxide (2%; 40 ml) for 20 min when a clear orange solution was obtained. Acidification precipitated a semi-solid from which the ketol (0·1 g), m.p. 220 °C, was obtained after several recrystallizations from ethyl acetate.

(iii) Methanolysis of the acetate (0·25 g) by the method in Section IX (*aa*) gave the ketol (0·15 g), m.p. 221 °C, after recrystallization from ethyl acetate.

(*dd*) *Reduction of the Ketol XXVIII*.—The ketol (0·08 g) in ethanol (20 ml) containing a trace of alkali was hydrogenated in the presence of a platinum catalyst at room temperature and pressure. After 1 hr the mixture was filtered, the filtrate neutralized with acetic acid, and evaporated under reduced pressure. Fractional crystallization of the residue from aqueous methanol gave the *trans*-glycol (0·003 g), m.p. and mixed m.p. 242–243 °C.

(*ee*) *Oxidation of* N-*Methylflindersine with Chromic Anhydride*.—A solution of chromic anhydride (0·63 g) in acetic acid (50%; 4 ml) was added during 6 hr to a stirred solution of *N*-methylflindersine (2·25 g) in glacial acetic acid (35 ml) at 40 °C. After standing overnight at room temperature the mixture was diluted and extracted with chloroform. The extract, after washing, was evaporated leaving an oil which solidified on contact with benzene-light petroleum. The trans-*glycol monoacetate* (XXIX) crystallized from methanol in small colourless needles (0·9 g), m.p. 201 °C (Found: C, 64·2; H, 6·0; N, 4·5%. Calc. for $C_{17}H_{19}O_5N$: C, 64·3; H, 6·0; N, 4·4%).

(*ff*) N-*Methylflindersine* trans-*Glycol* (*XXX*).—The ester (0·24 g) was deacetylated by sodium methoxide (from 0·04 g sodium) in methanol (15 ml) at room temperature for 8 hr as usual. The trans-*glycol* (0·15 g) crystallized from benzene-light petroleum in colourless needles, m.p. 178 °C (Found: C, 65·6; H, 6·3; N, 4·8%. Calc. for $C_{15}H_{17}O_4N$: C, 65·4; H, 6·2; N, 5·1%).

(*gg*) *Rearrangement to the Ketone XXXI*.—The *trans*-glycol XXX (0·1 g) on refluxing with sulphuric acid (10%; 20 ml) for 2 hr afforded the *ketone* (0·05 g) which crystallized from benzene-light petroleum in pale cream plates, m.p. 175 °C (Found: C, 70·4; H, 5·8; N, 5·4%. Calc. for $C_{15}H_{15}O_3N$: C, 70·0; H, 5·9; N, 5·4%).

(*hh*) *Flindersine* cis-*Glycol*.—Flindersine (1·79 g) was dissolved in pure dry benzene (50 ml) containing pure dry pyridine (1·25 ml) and osmium tetroxide (2 g) added. The mixture darkened and the reddish brown microcrystalline complex began to separate almost immediately. The reaction was slightly exothermic and the temperature was kept below 20 °C. After standing for 20 hr with occasional shaking, the complex was collected and dissolved in methylene chloride (50 ml). It was decomposed by shaking with potassium hydroxide (1%; 50 ml) containing mannitol (5 g) when some of the product separated. It was combined with the remainder isolated from the organic layer by evaporating under reduced pressure. The cis-*glycol* (1·8 g) crystallized from ethanol in colourless plates, m.p. 223 °C (Found: C, 64·7; H, 5·6; N, 5·6%. Calc. for $C_{14}H_{15}O_4N$: C, 64·4; H, 5·8; N, 5·4%).

Its rearrangement to the ketone XXVII was effected under the same conditions used for the *trans*-glycol.

(*ii*) *Lead Tetra-acetate Oxidations.*—(i) Flindersine *cis*-glycol (1·0 g) and lead tetra-acetate (2·1 g wet; equivalent to 10% excess) were shaken in glacial acetic acid (20 ml) containing 1% acetic anhydride at room temperature for 2 hr. By titration it had previously been found that the oxidation was complete in this time. The reaction mixture was then poured into sodium acetate (50%; 120 ml) containing potassium iodide (2·5 g). The liberated iodine was reduced with sodium thiosulphate and the mixture extracted with chloroform. The extract was washed with dilute sodium thiosulphate, sodium carbonate (5%; 3×50 ml) and water, and dried. Removal of the solvent left a crude product which on crystallization from either ethyl acetate, acetone, methanol, or chloroform gave colourless needles (0·25 g) of the *substance*, m.p. 178 °C. All samples of this substance were solvated and attempts to remove the solvent completely were unsuccessful. At 118 °C/1 mm the material slowly lost weight but gradually darkened. Representative analyses of the partially dried material were: C, 62·9, 61·3, 60·1; H, 6·4, 5·3, 6·2; N, 5·4, 5·4%. (Calc. for $C_{14}H_{13}O_4N$: C, 64·8; H, 5·0; N, 5·4%).

Acidification of the sodium carbonate extracts gave 4-hydroxy-2-quinolone-3-carboxaldehyde (0·45 g) which crystallized from glacial acetic acid in light tan needles, m.p. >360 °C (Found: C, 63·5; H, 3·8; N, 7·4%. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%). Its phenylhydrazone had m.p. and mixed m.p. with an authentic specimen 235 °C.

(ii) Flindersine *trans*-glycol (0·2 g) was oxidized as above in the dark for 72 hr, giving the substance (0·03 g), m.p. 178 °C, and 4-hydroxy-2-quinolone-3-carboxaldehyde (0·1 g). Purification of the former substance was more difficult in this case.

(iii) The ketol XXVIII (0·2 g) was oxidized as above in the dark for 150 hr. On working up as usual an insoluble solid and a chloroform extract were obtained. Recrystallization of the solid from glacial acetic acid gave 4-hydroxy-2-quinolone-3-carboxylic acid (0·05 g), m.p. 320 °C (decomp.), further identified by hydrolysis with acid to 4-hydroxy-2-quinolone. From the chloroform extract starting material (0·07 g) was recovered.

(*jj*) *Hydrolysis of the Substance, m.p. 178 °C.*—The substance (0·2 g) was heated under reflux with 10% hydrochloric acid for 15 min. After cooling and diluting, the precipitated 4-hydroxy-2-quinolone-3-carboxaldehyde (0·12 g) was filtered off and identified as in Section IX (*ii*). The filtrate was neutralized with dilute sodium carbonate, then made just acid with acetic acid and phenylhydrazine hydrochloride (0·5 g) and sodium acetate (0·8 g) added. The mixture was refluxed for 1 hr when an oil separated which solidified on standing. The product crystallized from benzene in pale cream needles (0·06 g), m.p. 242 °C, alone or mixed with authentic diacetyl phenylosazone (Found: C, 72·4; H, 6·9; N, 20·8%. Calc. for $C_{16}H_{18}N_4$: C, 72·2; H, 6·8; N, 21·0%).

(*kk*) *Periodate Oxidation of Flindersine cis-Glycol.*—A solution of the glycol (0·167 g) in ethanol (7 ml) was cooled to 10 °C and treated with water (10 ml) and periodic acid (0·154 N; 10 ml). The solution was shaken at room temperature for 20 min, neutralized with aqueous sodium bicarbonate, and treated with potassium iodide (20%; 2 ml). The liberated iodine was titrated with standard sodium arsenite (periodate used, 8·9 ml; calc. 8·3 ml). The crystalline precipitate was collected, washed, and recrystallized from aqueous methanol giving colourless needles (0·15 g), m.p. 126 °C, of the *dialdehyde* XXXIII (Found after drying at 65 °C/2 mm: C, 60·7; H, 5·6%. Calc. for $C_{14}H_{12}O_4N.H_2O$: C, 60·6; H, 5·5%. Found after drying at 100 °C/2 mm for 12 hr: C, 64·2; H, 5·3%. Calc. for $C_{14}H_{13}O_4N$: C, 64·9; H, 5·1%).

(*ll*) *Hydrolysis of the Dialdehyde (XXXIII).*—(i) Hydrolysis effected as in Section IX (*ii*) gave the same products in approximately the same yields.

(ii) The dialdehyde (0·2 g) was warmed on the water-bath for 5 min with sulphuric acid (N; 10 ml) and the mixture cooled. The 4-hydroxy-2-quinolone-3-carboxaldehyde (0·13 g) was collected and the filtrate treated with potassium periodate (0·2 g). After 20 min the mixture was distilled and the distillate collected in a saturated solution of 2,4-dinitrophenylhydrazine in 2N sulphuric acid. The product, acetone 2,4-dinitrophenylhydrazone (0·1 g), crystallized from ethanol in orange prisms, m.p. and mixed m.p. 124 °C (Found: C, 45·5; H, 4·4%. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2%).

(iii) The dialdehyde (0·2 g) was hydrolysed as in (ii) above, the 4-hydroxy-2-quinolone-3-carboxaldehyde collected, and the filtrate distilled rapidly into the dinitrophenylhydrazine reagent. The orange precipitate was purified by passing its benzene solution through a short column of alumina and recrystallization from ethanol. Long orange needles (0·1 g) of α-hydroxy-*iso*butyraldehyde 2,4-dinitrophenylhydrazone, m.p. 187 °C, were obtained (Found: C, 44·9; H, 4·5%. Calc. for $C_{10}H_{12}O_5N_4$: C, 44·8; H, 4·5%). Braude and Timmons (1953) give m.p. 188–191 °C.

(*mm*) *Chlorodeoxyflindersine* cis-*Glycol*.—Chlorodeoxyflindersine (0·9 g) was oxidized with osmium tetroxide (0·9 g) as in Section IX (*hh*). The *glycol* (0·6 g) isolated from the methylene chloride by extraction with 2% hydrochloric acid, crystallized from benzene in fine colourless needles, m.p. 194 °C (Found: C, 60·4; H, 5·4%. Calc. for $C_{14}H_{14}O_3NCl$: C, 60·1; H, 5·1%).

(*nn*) *N-Methylflindersine* cis-*Glycol*.—Oxidation of *N*-methylflindersine (0·95 g) by osmium tetroxide (1 g) as usual gave the cis-*glycol* (0·7 g) which crystallized from benzene-light petroleum in colourless needles, m.p. 160 °C (Found: C, 65·6; H, 6·2; N, 5·1%. Calc. for $C_{15}H_{17}O_4N$: C, 65·4; H, 6·2; N, 5·1%).

Rearrangement by acid to the ketone XXXI was effected by the same procedure used for the *trans*-glycol.

(*oo*) *Lead Tetra-acetate Oxidation of N-Methylflindersine* cis-*Glycol*.—The glycol (0·5 g) was oxidized with lead tetra-acetate for 2 hr as in Section IX (*ii*) (i). The sole product, isolated by diluting the reaction mixture and extracting with chloroform was the *aldehyde* XXXIV (0·25 g), which crystallized from methanol in colourless needles, m.p. 178 °C undepressed by admixture with a synthetic specimen (Found: C, 65·2; H, 4·4; N, 7·0%. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5; N, 6·9%).

The *phenylhydrazone* crystallized from ethanol in yellowish needles, m.p. 235 °C undepressed by the synthetic substance (Found: C, 69·6; H, 5·3%. Calc. for $C_{17}H_{15}O_2N_3$: C, 69·6; H, 5·2%).

(*pp*) *Synthesis of 4-Hydroxy-1-methyl-2-quinolone-3-carboxaldehyde*. — Chloroform (14 g) was added during 3 hr to a stirred solution of 4-hydroxy-1-methyl-2-quinolone (1 g) in sodium hydroxide (15%; 80 ml) heated on the water-bath. The mixture was cooled, the product collected, and recrystallized from methanol with the aid of charcoal as pale brown needles, m.p. 178 °C (Found: C, 65·1; H, 4·5%. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5%). The phenylhydrazone had m.p. 235 °C.

(*qq*) *Ozonolysis of N-Methylflindersine*.—A stream of ozonized oxygen was passed through a solution of *N*-methylflindersine (0·6 g) in ethyl acetate at —25 °C for 30 min. The solid which separated was collected, suspended in ethyl acetate, and hydrogenated in the presence of palladium-charcoal. When absorption of hydrogen ceased, the mixture was filtered and the filtrate evaporated under reduced pressure. The residue crystallized from methanol in slightly purplish needles (0·08 g), m.p. and mixed m.p. with 4-hydroxy-1-methyl-2-quinolone-3-carboxaldehyde, 178 °C (Found: C, 64·9; H, 4·3%. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5%).

(*rr*) *Preparation of the Amides XXXVII and XXXVIII*.—(i) Methyl anthranilate (3·6 g) was added to dimethyl malonate (20 ml) at 180 °C and the mixture gently refluxed for 2 hr. Excess dimethyl malonate was removed under reduced pressure and the residue stirred with ether when it crystallized. The *diamide* XXXVII (2 g) separated from methanol as colourless needles, m.p. 148–149 °C (Found: C, 61·8; H, 4·8%. Calc. for $C_{19}H_{18}O_6N_2$: C, 61·6; H, 4·9%).

(ii) Methyl anthranilate (3 g) and dimethyl malonate (30 ml) were heated at 150 °C for 2 hr and then the temperature slowly raised to 180 °C during a further 2 hr. Excess dimethyl malonate was distilled off under reduced pressure and the residue stirred with a little ether when it solidified. Several recrystallizations from methanol gave colourless plates (3·4 g) of the *monoamide* XXXVIII, m.p. 90 °C (Found: C, 57·7; H, 5·3; N, 5·8; OCH_3, 24·1%. Calc. for $C_{12}H_{13}O_5N$: C, 57·4; H, 5·2; N, 5·6; $2\times OCH_3$, 24·7%).

(*ss*) *Cyclization of the Amides XXXVII and XXXVIII*.—(i) A boiling solution of the diamide (2 g) in dry methanol (30 ml) was treated with a solution of sodium methoxide (from 0·4 g sodium) in dry methanol (20 ml). Most of the methanol was removed by distillation and water and acetic

acid added to the residue when a crystalline product (1·7 g) separated. Recrystallization from a large volume of acetone gave colourless needles, m.p. 242–243 °C, of the *amido-ester* XXXIX (Found : C, 63·7 ; H, 4·2 ; OCH_3, 9·1%. Calc. for $C_{15}H_{14}O_5N_2$: C, 63·9 ; H, 4·2 ; $1\times OCH_3$, 9·2%).

(ii) The monoamide (2 g) was cyclized by sodium methoxide (from 0·4 g sodium) in methanol as above. The crystalline sodio-derivative, isolated by adding ether to the reaction mixture, was decomposed by dilute acetic acid. The methyl ester XL crystallized from acetone in colourless needles (1·45 g), m.p. and mixed m.p. with the product from the methanolysis of flindersinic acid or with the substance prepared by the method of Asahina, Ohta, and Inubuse (1930), 225 °C (Found : C, 60·2 ; H, 4·1%. Calc. for $C_{11}H_9O_4N$: C, 60·3 ; H, 4·1%).

(iii) Cyclization of the monoamide by sodium ethoxide in dry ethanol and working up as in (ii) above gave the ethyl ester VII which crystallized from acetone in colourless needles, m.p. and mixed m.p. with the product from the ethanolysis of flindersinic acid or with the product from the esterification with ethanol of 4-hydroxy-2-quinolone-3-carboxylic acid or with the product obtained from the reduction of diethyl *o*-nitrobenzoylmalonate, 208 °C (Found : C, 61·8 ; H, 4·7 ; OC_2H_5, 19·2%. Calc. for $C_{13}H_{11}O_4N$: C, 61·8 ; H, 4·8 ; $1\times OC_2H_5$, 19·3%).

(*tt*) *Reductive Cyclization of Diethyl* o-*Nitrobenzoylmalonate.*—(i) Granulated zinc (9 g) was added to a solution of the ester (3·5 g) in dry ethanol (35 ml) and a rapid stream of dry hydrogen chloride passed in. When all the zinc had dissolved the red solution was filtered and poured into water (500 ml). The red precipitate was collected, washed well with water, and allowed to stand overnight with aqueous ethanolic potassium hydroxide (5% ; 50 ml). Acidification with dilute acetic acid gave a precipitate which after repeated recrystallization from ethanol afforded colourless needles (0·6 g) of the ethyl ester VII, m.p. and mixed m.p. 208 °C (Found : N, 6·2 ; OC_2H_5 19·5%. Calc. for $C_{12}H_{11}O_4N$: N, 6·0 ; $1\times OC_2H_5$, 19·3%).

(ii) The red precipitate referred to above, on repeated recrystallization from ethanol with the aid of charcoal gave colourless needles (0·7 g) of the ethyl ester VII m.p. and mixed m.p. 208 °C.

(iii) The ester (2 g) was dissolved in dry ethanol (35 ml) and the solution saturated with dry hydrogen chloride. Granulated zinc (6 g) was added and passage of the hydrogen chloride continued until the zinc had dissolved. The filtered solution was diluted, the mixture basified with ammonia, and then acidified with acetic acid. On standing a red precipitate was obtained which was separated into a fraction soluble in and a fraction insoluble in hot ethanol. Concentration of the ethanol extract gave crystals which were repeatedly recrystallized from ethanol with the aid of charcoal. The product XXXV formed colourless leaflets (0·2 g), m.p. 103 °C (Found : C, 64·0 ; H, 5·8 ; OC_2H_5, 33·6%. Calc. for $C_{14}H_{15}O_4N$: C, 64·4 ; H, 5·8 ; $2\times OC_2H_5$, 34·4%).

The ethanol-insoluble fraction, which contained zinc, was decomposed with dilute hydrochloric acid, and the product recrystallized from ethanol. The cyclic *hydroxamic acid* (XLI) (0·3 g) formed long pale yellow needles, m.p. 165 °C (Found : C, 57·8 ; H, 4·5 ; OC_2H_5, 18·2%. Calc. for $C_{12}H_{11}O_5N$: C, 57·8 ; H, 4·5 ; $1\times OC_2H_5$, 18·1%).

(*uu*) *Hydrolysis of the Ester XXXV.*—(i) The substance (0·1 g) was heated under reflux with hydrochloric acid (5N ; 10 ml) for 2 hr. The solution was cooled and nearly neutralized by the addition of dilute ammonia. On standing 4-hydroxy-2-quinolone (0·03 g) separated and was identified in the usual way.

(ii) The ester (0·15 g) was dissolved in a solution of potassium hydroxide (0·6 g) in water (3 ml) and the solution heated at 90 °C for 45 min. Acidification with dilute acetic acid gave a precipitate which was recrystallized from glacial acetic acid. The product (0·1 g) which formed small pale yellow needles, m.p. 163–164 °C (decomp.) could not be obtained analytically pure, presumably because of partial decarboxylation.

The acid (0·2 g) was heated in an oil-bath at 180 °C until evolution of carbon dioxide ceased. Crystallization of the residue from ethyl acetate gave small, pale yellow cubes (0·1 g) of *2-ethoxy-4-hydroxyquinoline*, m.p. 174–175 °C (Found : C, 69·8 ; H, 6·0 ; OC_2H_5, 22·0%. Calc. for $C_{11}H_{11}O_2N$: C, 69·8 ; H, 5·9 ; $1\times OC_2H_5$, 23·8%).

The phenol (0·015 g) in ethanol (1 ml) was treated with excess ethereal diazoethane for 1 hr. The product crystallized from aqueous ethanol in colourless leaflets, m.p. 54 °C undepressed by admixture with an authentic specimen of 2,4-diethoxyquinoline (Buchmann and Hamilton 1942). The *picrate*, yellow needles from ethanol (Found : N, 12·7%. Calc. for $C_{19}H_{18}O_9N_4$: N, 12·6%) had m.p. 192–193 °C alone or mixed with authentic 2,4-diethoxyquinoline picrate.

(*vv*) *Ethylation of the Ester VII.*—The ester (0·4 g) suspended in ethanol (10 ml) was treated with ethereal diazoethane which was added in portions until the solid dissolved. The reaction mixture on working up as above gave the *ester* XLII which crystallized from ethanol in colourless needles (0·3 g), m.p. 173–174 °C (Found : C, 64·8 ; H, 6·1 ; OC_2H_5, 34·9%. Calc. for $C_{14}H_{15}O_4N$: C, 64·4 ; H, 5·8 ; OC_2H_5, 34·4%).

(*ww*) *Methylation of the Ester VII.*—Methylation with excess diazomethane for 20 hr gave a substance, m.p. 163 °C, which contained 20·5% nitrogen. It was not further examined. However, methylation under the conditions of Section IX (*vv*) using methanol gave the ester XLIII which crystallized from ethyl acetate in colourless plates, m.p. 145 °C (Found : N, 5·9 ; OCH_3, 25·5%. Calc. for $C_{13}H_{13}O_4N$: N, 5·7 ; $1\times OCH_3+1\times OC_2H_5$ (as OCH_3), 25·1%). Hydrolysis with dilute acid gave 4-hydroxy-2-quinolone.

(*xx*) *Dictamnic Acid* (*XLIV*).—The ester XLIII (0·15 g) was hydrolysed with aqueous potassium hydroxide as in Section IX (*uu*) (ii). The dictamnic acid (0·1 g) crystallized from methanol in colourless needles, m.p. and mixed m.p. with an authentic specimen 260 °C (decomp.) (Found : C, 60·1 ; H, 4·3 ; OCH_3, 14·4%. Calc. for $C_{11}H_9O_4N$: C, 60·3 ; H, 4·1 ; $1\times OCH_3$, 14·1%).

(*yy*) *Methylation of the Ester XL.*—The ester XL was methylated as in (*ww*). The *product* crystallized from ethyl acetate in colourless needles, m.p. 186 °C (Found : C, 61·8 ; H, 4·9%. Calc. for $C_{12}H_{11}O_4N$: C, 61·8 ; H, 4·8%), not depressed by methyl dictamnate prepared from authentic dictamnic acid by methylation by the same procedure.

(*zz*) *3-(2′-Carboxyethyl)-4-hydroxy-2-quinolone* (*III*).—A solution of triethyl propane-1,1,3-tricarboxylate (11·4 g) in pure dry benzene (15 ml) was refluxed with powdered sodium (1 g) until it had dissolved (*c.* 5 hr). The cooled mixture was then treated with a solution of distilled *o*-nitrobenzoyl chloride (7·4 g) in benzene (10 ml) added gradually with shaking. After standing overnight, the reaction mixture was refluxed for 5 hr, then cooled, and shaken with aqueous sodium carbonate and water. The benzene was distilled off and as much unreacted ester as possible removed by distillation at 1 mm. The residue (8 g) was added in portions to a mixture of boiling concentrated hydriodic acid (30 ml) and red phosphorus (2·5 g) and the whole refluxed for 30 min. The mixture was diluted, filtered, and the precipitate extracted with dilute sodium bicarbonate. Acidification of the extract gave the required acid III (1·6 g) which after repeated recrystallization from methanol formed colourless needles, m.p. 314 °C (Found : C, 62·1 ; H, 5·1 ; N, 5·9%. Calc. for $C_{12}H_{11}O_4N$: C, 61·8 ; H, 4·8 ; N, 6·0%).

(*aaa*) *3-(1′-Carboxyethyl)-4-hydroxy-2-quinolone* (*IV*).—This was prepared by the same method as above from triethyl propane-1,1,2-tricarboxylate. The *acid* IV crystallized from methanol in colourless needles, m.p. 304 °C (Found : C, 62·1 ; H, 5·1 ; N, 5·8%. Calc. for $C_{12}H_{11}O_4N$: C, 61·8 ; H, 4·8 ; N, 6·0%).

(*bbb*) *4-Hydroxy-3-(2′-methylbutyl)-2-quinolone.*—This *substance* prepared by the same method from diethyl 3-methylbutane-1,1-dicarboxylate crystallized from ethyl acetate in colourless needles, m.p. 201 °C (Found : C, 73·1 ; H, 7·6 ; N, 6·4%. Calc. for $C_{14}H_{17}O_2N$: C, 72·7 ; H, 7·4 ; N, 6·1%).

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THE ALKALOIDS OF *SENECIO JACOBAEA* L.

I. ISOLATION OF THE ALKALOIDS AND IDENTIFICATION OF JACODINE AS SENECIPHYLLINE

By R. B. BRADBURY* and C. C. J. CULVENOR*

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Summary

The following five alkaloids have been isolated from *Senecio jacobaea* L. (ragwort): seneciphylline, $C_{18}H_{23}O_5N$; jacobine, $C_{18}H_{25}O_6N$; jacozine, $C_{18}H_{23}O_6N$; jaconine, $C_{36}H_{32}O_7NCl$; and jacoline, $C_{18}H_{27}O_7N$. Jacodine which has been identified as seneciphylline, jacobine and jaconine have been isolated from this species by earlier workers, but jacozine and jacoline are new alkaloids.

I. INTRODUCTION

The early literature concerning the pharmacological and chemical properties of the alkaloids from *Senecio jacobaea* L., commonly known as ragwort, has been adequately summarized by Hosking and Brandt (1936). In common with other *Senecio* bases, the ragwort alkaloids are capable of producing liver cirrhosis in animals, and in view of the widespread occurrence of this plant as a pasture weed in Gippsland and the Otway Ranges of Victoria, it was considered desirable to examine the constituent alkaloids more thoroughly.

The first important investigation of the alkaloids of *S. jacobaea* was made by Manske (1931), who obtained a compound, m.p. 223–224 °C, which analysed poorly for $C_{18}H_{23}O_5N$. Hosking and Brandt (loc. cit.) isolated a compound $C_{18}H_{25}O_6N$, m.p. 219 °C, $[\alpha]_D^{12}$ −130·2°, and Barger and Blackie (1937) a compound of the same melting point but of lower rotation ($[\alpha]_D^{17}$ −46·3 and −30·5°) from *S. jacobaea* and *S. cineraria* DC. Both compounds were claimed to be identical with the jacobine of Manske. Two other compounds, jacodine, $C_{18}H_{25}O_5N$, m.p. 217 °C, $[\alpha]_D^{17}$ −109·6°, and jaconine, $C_{18}H_{25}O_8N$, m.p. 146 °C, were also reported by Barger and Blackie (loc. cit.).

In the present work jacodine and jacobine could be obtained from some samples of the crude bases by repeated recrystallization from ethanol, and jaconine could be consistently isolated in the pure state by recrystallization of the mixed hydrochlorides from ethanol, but the separation, particularly of the two new bases jacozine and jacoline, by these methods proved ineffective. Adams and Govindachari (1949*a*, 1949*b*) and Adams and Looker (1951) have previously emphasized the difficulties encountered in the separation of closely related *Senecio* alkaloids. These workers made use of chromatography on alumina, but in the present investigation a better separation was obtained on

* Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

columns of buffered kieselguhr and particularly on powdered cellulose. Paper chromatography was used throughout to determine the composition of the alkaloid fractions and to check the purity of compounds isolated.

Young plants of *S. jacobaea* collected at Foster, Victoria, in August 1953 were assayed by the procedure previously used by Culvenor, Drummond, and Price (1954) for the bases from *Heliotropium europaeum* L. Passage of the bases through a buffered kieselguhr column resulted in only partial resolution, but approximate values for the proportion of individual bases in the mixed fractions were obtained by paper chromatography. The percentages of alkaloids present, their empirical formulae, and physical constants are given in Table 1.

TABLE 1

EMPIRICAL FORMULAE, PHYSICAL CONSTANTS, AND PERCENTAGE CONTENT OF THE ALKALOIDS OF SENECIO JACOBAEA

Alkaloid	Empirical Formula	M.P. (°C)	$[\alpha]_D$ (deg)	R_F Value	Dry Wt. (%)
Seneciphylline (jacodine)	$C_{18}H_{23}O_5N$	217	—139*	0·52	0·036
Jaconine	$C_{20}H_{32}O_7NCl$	147	+52†	0·43	0·018
Jacobine	$C_{18}H_{25}O_6N$	228	—40*	0·39	0·078
Jacozine	$C_{18}H_{23}O_6N$	228	—140*	0·32	0·035
Jacoline	$C_{18}H_{27}O_7N$	221	+48*	0·26	0·009

* Chloroform.

† Ethanol.

Senecio jacobaea from Mirboo North, collected just before flowering, contained 0·3 per cent. crude base, from which jacobine, m.p. 220 °C, $[\alpha]_D^{26}$ —57°, was obtained by recrystallization from ethanol. Other plant samples, however, yielded jacobine only after chromatography of the crude bases, and a sample obtained from a cellulose column had m.p. 228 °C, $[\alpha]_D^{22}$ —40°. Since some analytically pure samples of smaller laevorotation, but with the same R_F value and melting point as jacobine have been obtained, it is possible that a diastereoisomer is produced in the plant, or during isolation of the base. The formula for jacobine, $C_{18}H_{25}O_6N$, given by Barger and Blackie (loc. cit.) has been confirmed, and this compound has been shown to be different from the isomeric retrorsine.

The residual alkaloid after removal of most of the jacobine by crystallization was chromatographed on kieselguhr at pH 8·0 and yielded in the carbon tetrachloride-chloroform fraction a compound, m.p. 216–217 °C, $[\alpha]_D^{26}$ —139°, which was probably identical with the jacodine obtained by Barger and Blackie (loc. cit.), but analysed according to the formula $C_{18}H_{23}O_5N$ rather than $C_{18}H_{25}O_5N$. The calculated analytical values reported by these workers for the last formula were incorrect, and it is possible that their compound was impure. The specimen isolated by the authors was shown by mixed melting point and infra-red absorption to be identical with seneciphylline (α-longilobine), the structure of which has been determined by Adams and Govindachari (1949*a*) and Adams *et al.* (1952). To avoid confusion it is suggested that the name, seneciphylline, which

has precedence (Orekhov and Tiedebel 1935), be retained in preference to α-longilobine or jacodine.

A compound, m.p. 147 °C, which may be identical with the base called jaconine by Barger and Blackie (loc. cit.), could be obtained by chromatography of the crude alkaloids on alumina, but more readily by crystallization of the crude hydrochlorides from ethanol. Because of its low solubility in ethanol compared with the hydrochlorides of the other bases, jaconine hydrochloride could be separated in high yield. The free base contains chlorine, $C_{20}H_{32}O_7NCl$, which was apparently overlooked by Barger and Blackie, and is unique among the *Senecio* alkaloids in this respect. Sceleratinic dilactone, $C_{10}H_{13}O_4Cl$, has been isolated by de Waal, Serfontein, and Garbers (1951) from *S. sceleratus* Schweikert, but it was not found in combination as an alkaloid. Jaconine undoubtedly occurs in the plant since its recovery was unaffected by the use of sulphuric acid instead of hydrochloric acid, and by extraction with purified acid-free solvents.

Chromatography of the crude alkaloids on acid-washed alumina yielded in the chloroform-ether eluates mainly seneciphylline, and in the chloroform eluates mainly jacobine, but the separation of these compounds was poor. However, the 1 per cent. ethanol-chloroform eluates regularly showed spots on paper of R_F 0·32 (jacobine 0·39). One of these fractions when recrystallized many times from ethanol and ethyl acetate yielded colourless plates, m.p. 222–223 °C, $[\alpha]_D^{28}$ −127°, and analysed according to the formula $C_{18}H_{25}O_7N$. It is the hydrate of a new base called jacozine. Jacozine is readily obtained in a pure state by chromatography of concentrates on a cellulose column and has m.p. 228 °C (decomp.), $[\alpha]_D^{22}$ −140°. This base, not detected by earlier workers appears to be a major constituent of the plant. The 5 and 10 per cent. ethanol-chloroform eluates from the alumina column yielded almost pure fractions of an alkaloid, m.p. 221–222 °C, $[\alpha]_D^{24}$ +48·2°, analysing for $C_{18}H_{27}O_7N$. This compound has been called jacoline, and may also be isolated in essentially pure form by chromatography on buffered kieselguhr. No definite evidence was obtained for the presence of *N*-oxides, and none of the bases isolated were *N*-oxides, since they were unaffected by zinc and sulphuric acid.

II. Experimental

All melting points are corrected. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory.

(*a*) *Isolation of the Crude Bases.*—Dried tops of *S. jacobaea* collected just before flowering at Mirboo North, Victoria, in the spring of 1952 (dry wt. 7·25 kg) were milled and extracted with methanol, and the concentrate (1500 ml) was diluted with water (1000 ml) and concentrated hydrochloric acid (100 ml) added. The mixture was extracted with chloroform, the chloroform extract washed once with aqueous hydrochloric acid (5%; 400 ml) and the chloroform phase discarded. The combined aqueous extracts were basified with ammonia and extracted with chloroform (8 × 250 ml). This chloroform extract was again taken into acid and the bases liberated on making alkaline and re-extracted with chloroform. After drying over sodium sulphate and removal of the chloroform, crude solid base (18·7 g, 0·26%) was obtained.

(*b*) *Jacobine.*—Repeated recrystallization of the crude base from ethanol and methanol gave colourless plates (8·5 g), m.p. 220 °C, $[\alpha]_D^{26}$ −57° (*c*, 1·7 in chloroform), showing depression in

melting point when admixed with retrorsine (Found: C, 61·8; H, 6·9; N, 4·4%; equiv. (by titration), 345. Calc. for $C_{18}H_{25}O_6N$: C, 61·5; H, 7·2; N, 4·0%; equiv. wt., 351). Another sample, obtained by chromatography on cellulose (see under jacozine, Section II (*f*)), separated from ethanol in plates, m.p. 228 °C (slight decomp., in evacuated tube), $[\alpha]_D^{22}$ —40° (*c*, 1·13 in chloroform).

(*c*) *Seneciphylline* (*jacodine*, *α-longilobine*).—The mother liquors from the crystallization of jacobine were evaporated and the resulting base (7·7 g) chromatographed on a column of kieselguhr ("Hyflo-Super-Cel"; 200 g), moistened with phosphate buffer (120 ml) at pH 7·5. Eluting solvents used were: (1) 80% light petroleum-carbon tetrachloride, (500 ml); (2) 20% light petroleum-carbon tetrachloride (600 ml); (3) carbon tetrachloride (1000 ml); (4) 80% carbon tetrachloride-chloroform (1000 ml); (5) 20% carbon tetrachloride-chloroform (850 ml); (6) chloroform (2000 ml).

Eluates of 50 ml were collected and 1 ml aliquots titrated with 0·01N *p*-toluenesulphonic acid in chloroform to determine the position of elution of the bases. A more detailed description of the procedure used with this type of column has been given in an earlier paper (Culvenor, Drummond, and Price 1954). Fractions were combined according to the peaks of the elution curve and the alkaloid composition of the recovered bases determined by paper chromatography. Fractions 19–28 (1·16 g), which showed a strong spot at R_F 0·52 (seneciphylline) and a weak spot at R_F 0·39 (jacobine), furnished colourless prisms from ethanol (0·28 g), m.p. 216–217 °C, depressed on admixture with jacobine, $[\alpha]_D^{26}$ —139° (*c*, 1·27 in chloroform) (Found: C, 65·0; H, 6·9; N, 4·5%; equiv. (by titration), 331. Calc. for $C_{18}H_{23}O_5N$: C, 64·8; H, 6·9; N, 4·2%; equiv. wt., 333). Seneciphylline gave no depression with α-longilobine and the two substances showed identical absorption bands, differing only slightly in intensity. Fractions 33–53 (1·57 g) which showed a strong spot at R_F 0·39 and a weak spot at R_F 0·52, when recrystallized from ethanol yielded colourless plates, m.p. 219 °C, undepressed when admixed with the jacobine obtained above. Concentrates of the other three bases were obtained, but only these two eluates yielded pure bases on recrystallization.

(*d*) *Jacoline*.—A part (12·8 g) of the crude alkaloid (0·39%; 29·1 g) obtained from another sample of ragwort (dry wt. 7·5 kg) collected at Foster, Victoria, in August 1953 was chromatographed on acid washed alumina (200 g). The early fractions contained seneciphylline, jacobine, and jacozine, but the 10% ethanol-chloroform eluate yielded a solid (0·62 g), which when recrystallized from ethanol yielded pure *jacoline*, m.p. 221·5 °C, showing depression in melting point on admixture with seneciphylline and jacobine $[\alpha]_D^{24}$ +48° (*c*, 1·155 in chloroform) (Found: C, 58·5; H, 7·5; N, 3·9; O, 30·5%; equiv. (by titration), 374. Calc. for $C_{18}H_{27}O_7N$: C, 58·5; N, 7·4; N, 3·8; O, 30·3%; equiv. wt., 369).

(*e*) *Jaconine*.—The combined alkaloid residues from the previous fractions (11·5 g) were dissolved in ethanol (30 ml) in an evaporating basin, and concentrated hydrochloric acid (4 ml) in water (50 ml) added dropwise to the solution, which was evaporated to dryness *in vacuo* over solid sodium hydroxide. On warming with ethanol (100 ml) and cooling, a crystalline hydrochloride (5·8 g), m.p. 205–206 °C, was obtained, which on recrystallization from ethanol gave *jaconine hydrochloride* as colourless needles, m.p. 207 °C (with effervescence) (Found: C, 51·4; H, 7·0; N, 3·2; Cl, 15·4%. Calc. for $C_{29}H_{33}O_7NCl_2$: C, 51·1; H, 7·1; N, 3·0; Cl, 15·1%).

The above hydrochloride (6·8 g) was dissolved in water (20 ml) and basified with ammonia. The separated solid was filtered, dried (4·4 g, m.p. 145 °C), and recrystallized from ethanol to give jaconine as colourless prisms, m.p. 147 °C, $[\alpha]_D^{20}$ +52·5° (*c*, 1·144 in ethanol) (Found: C, 55·4; H, 7·2; N, 3·5; O, 25·7; Cl, 8·4%; equiv. (by titration), 431. Calc. for $C_{29}H_{32}O_7NCl$: C, 55·4; H, 7·4; N, 3·2; O, 25·8; Cl, 8·2%; equiv. wt., 434).

(i) *Isolation of Jaconine without the Use of Hydrochloric Acid*. The crude base (4·2 g) was isolated by extracting the concentrate from methanol extraction of the plant with dilute sulphuric acid, reducing the aqueous solution with zinc dust, filtering, basifying with ammonia, and extracting with acid-free trichloroethylene. This base was chromatographed on cellulose (450 g; in a column 5 by 80 cm) using butanol-acetic acid as solvent, under conditions similar to those described below for jacozine. Eluates shown by paper chromatography to contain

jaconine were combined and the free base recovered from the acetate. The product (0·58 g) on recrystallization from ethanol furnished jaconine, m.p. and mixed m.p. 147 °C.

(*f*) *Jacozine.*—Chromatography of the crude alkaloid mixtures on alumina consistently yielded eluates with 1% ethanol-chloroform in which paper chromatograms showed the presence of an alkaloid of R_F 0·31. These concentrated fractions were separated satisfactorily by chromatography on cellulose. The solvent was prepared as for paper chromatography, that is, by shaking butanol with an equal volume of acetic acid (5%); the upper layer constituted the eluting solvent. A portion of the aqueous phase (50 ml) was used to premoisten the cellulose powder (125 g) by shaking together with the eluting solvent (1 l.). The cellulose was packed as a slurry

TABLE 2

CHROMATOGRAPHY ON CELLULOSE-ISOLATION OF JACOZINE

Fraction	Wt. of Fraction (g)	R_F Values (%)	Base Indicated
1– 9	0·00	—	—
11	0·02	0·53	Seneciphylline
13	0·05	0·52	,,
15	0·05	0·52	,,
17	0·13	0·36	Jacobine
19	0·13	0·37, 0·30 (Very weak)	Jacobine, trace of jacozine
21	0·14	0·30	Jacozine
23	0·10	0·30	,,
25	0·08	0·30	,,
27	0·05	0·30	,,
29	0·04	0·29	,,
31	0·06	0·30	,,
33	0·07	0·30	,,
35	0·01	0·30	,,
37	0·02	0·31	,,
39	0·04	0·31	,,
41	0·01	0·30, 0·22 (Weak)	Jacozine, a little jacoline
43	0·01	0·30, 0·22	Jacozine, jacoline
45	0·01	0·23	Jacoline
47–55	0·05	0·23	,,
56–80	0·03	0·22	,,

into a column 2·2 by 80 cm, tamping at intervals with a close fitting perforated plunger. Additional solvent (1 l.) was passed through the column to ensure equilibration before application of the alkaloid (1·4 g jacozine concentrates, converted into acetates). After a forerun of approximately 120 ml, eluates of 10 ml were collected, each fraction was evaporated *in vacuo*, and the R_F value determined. The results shown in Table 2 indicate a virtually complete separation of the constituents despite the comparatively high loading.

The base recovered from the combined fractions 11–15 when recrystallized from ethanol gave seneciphylline as colourless prisms, m.p. and mixed m.p. 217 °C. Fractions 17–19 gave plates from ethanol, m.p. 228 °C, $[\alpha]_D^{22}$ —40° (*c*, 1·13 in chloroform) undepressed on admixture with jacobine, but depressed (m.p. 212 °C) on admixture with jacozine. Fractions 21–39 furnished *jacozine* (0·57 g) which crystallized from ethanol as tabular prisms, m.p. 228 °C (slight decomp., in evacuated tube), $[\alpha]_D^{21}$ —140° (*c*, 1·90 in chloroform) (Found: C, 62·3; H, 6·7; N, 4·1; O, 27·0%. Calc. for $C_{18}H_{29}O_6N$: C, 61·9; H, 6·6; N, 4·0; O, 27·5%).

A fraction from alumina containing mainly this compound when repeatedly recrystallized from ethanol and finally ethyl acetate yielded jacozine as large colourless rectangular plates, m.p. 222–223 °C, $[\alpha]_D^{28}$ −127° (*c*, 0·883 in chloroform) (Found: C, 58·7; H, 6·7; N, 4·1; O, 30·5%. Calc. for $C_{18}H_{23}O_6N.H_2O$: C, 58·8; H, 6·9; N, 3·8; O, 30·5%). The analyses reported were obtained on a sample which was dried *in vacuo* over phosphorus pentoxide to remove any adhering solvent, and then allowed to stand for some days in the air. Attempts to determine the loss in weight on drying at 110 °C *in vacuo* over phosphorus pentoxide resulted in sublimation of the alkaloid.

(*g*) *Assay of Foster Sample of* S. jacobaea.—From air-dried tops (2·81 kg) the crude alkaloid (9·47 g; $1·8 \times 10^{-2}$ equiv., by titration) was isolated in the usual way with chloroform, and the residual aqueous solution was reduced with zinc and sulphuric acid, basified, and re-extracted with chloroform to give an additional quantity of base (0·75 g; $6·2 \times 10^{-4}$ equiv.). Both portions of the base were assayed according to the procedure described by Culvenor, Drummond, and Price (1954) for the assay of *H. europaeum*. The small amount of base obtained after reduction, and the fact that it was shown by assay to consist mainly of jacozine and jacoline, suggests that this material represents tertiary bases incompletely removed in the first extraction rather than *N*-oxide content. Results quoted (Table 1) comprise the sum of the two assays; the *N*-oxides thus represent less than 5% of the total alkaloid. The assay column was prepared from kieselguhr (20 g), and pH 8·0 buffer solution (8 ml), and the eluting solvents were: (1) 60% light petroleum-carbon tetrachloride (100 ml); (2) 20% light petroleum-carbon tetrachloride (80 ml); (3) carbon tetrachloride (65 ml); (4) 60% carbon tetrachloride-chloroform (70 ml); (5) chloroform (180 ml). Fractions were combined as indicated by the elution curve and the alkaloids present determined by paper chromatography. When more than one base was present in one peak, the proportions of each were estimated from the sizes of the spots, but by this procedure the accuracy might not be better than 10%. The results are shown in Table 1.

(*h*) *Paper Chromatography.*—Papers were run with ascending solvent which was the upper phase resulting from the equilibration of equal volumes of butanol and aqueous acetic acid (5%). The printing agent was iodine vapour. The chromatography tank was housed in a room which had a temperature variation during 24 hr of not more than 1 °C, and papers were allowed to equilibrate for at least 3 hr before starting the solvent flow. Under these conditions resolution was good and R_F values were reproducible to $\pm 0·02$.

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ASARININ IN *ACRONYCHIA MUELLERI* W. D. FRANCIS

By J. B. DAVENPORT* and M. D. SUTHERLAND†

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Summary

(+)-Asarinin has been found in the leaves of *Acronychia muelleri* W. D. Francis. An anomaly in the ultraviolet absorption of asarinin and of its diastereoisomer sesamin is discussed.

I. INTRODUCTION

(+)-Asarinin has been found in the leaves of *Acronychia muelleri* W. D. Francis, a tree of the family Rutaceae which grows in the north Queensland rain-forests. The (+)-form has not previously been found in plants, although the (−)-form occurs in *Asarum blumei* Duch. (Huang-Minlon 1937), *A. sieboldii* Miq. (Chou and Chu 1935), *Xanthoxylum carolianum* Lam. (Dieterle and Schwengler 1939) and *X. clava-herculis* L. (La Forge and Barthel 1944). (+)-Asarinin has been previously obtained by the isomerization of (+)-sesamin isolated from sesame oil and our material from *A. muelleri* appears to differ in no significant way from the literature description of (+)-asarinin. It is apparently unusual for lignanes to occur in leaves (Haworth 1942), as in this instance.

A difficulty met in measuring the ultraviolet absorption of asarinin with a Beckman DU spectrophotometer is of interest. It was found that the extinction coefficients at the maxima differed very considerably when calculated from optical densities measured on solutions of different concentrations. A plot of optical density *versus* concentration for a number of wavelengths (Fig. 1) showed that as the concentration increased, the density lost its proportionality to the concentration and finally became independent. Similar behaviour is shown by several fluorescent substances investigated by Braude, Fawcett, and Timmons (1950), including styryldimethyl carbinol which resembles asarinin in showing no fluorescence in the visible region. This phenomenon has recently been fully discussed (Braude and Timmons 1953; Ovenston 1953).

Although recent papers describing a spectrophotometric method for the determination of sesamin in sesame oil (Budowski, O'Connor, and Field 1951; Suarez *et al.* 1952) made no mention of this phenomenon, examination has revealed that the behaviour of sesamin (Fig. 1) is similar to that of asarinin. Erroneous values for sesamin content would result from the use of solutions of high optical density only.

* Division of Food Preservation and Transport, C.S.I.R.O., Homebush, N.S.W.

† Chemistry Department, University of Queensland.

II. Experimental

Melting points are uncorrected.

(*a*) *Isolation of* (+)-*Asarinin.*—The powdered leaves (25 g) containing 10·8% moisture (loss on heating at 100 °C for 2 hr) were exhaustively extracted with benzene in a Soxhlet apparatus and the extract was chromatographed on alumina. The eluate was collected in fractions of approximately 50 ml and each was evaporated and examined separately. The earlier fractions contained a white amorphous solid which, after several recrystallizations from ethanol and from acetone, sintered at 62 °C and melted at 73 °C, the yield being 10 mg (Found : C, 82·1, 81·9 ; H, 13·7, 14·0%). Following this, asarinin was obtained in a fairly pure state, the yield being 164 mg (0·66%). A more strongly absorbed substance of m.p. 126·5–127 °C was next eluted and will be reported on separately.

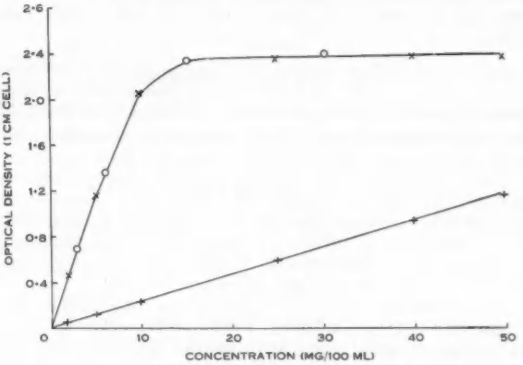

Fig. 1.—The effect of concentration on optical density.
×——× Asarinin at 287 mμ.
+——+ Asarinin at 255 mμ.
o——o Sesamin at 287 mμ.

Larger quantities were obtained as follows : the leaves were exhaustively extracted with benzene. On standing the benzene extract deposited crystals of the substance of m.p. 126·5–127 °C. Upon concentration of the mother liquors, asarinin crystallized and was filtered off. Recrystal ization from ethanol yielded white needles, m.p. 120–121 °C, $[\alpha]_D^{28}$ +117±1° (*c*, 3·7 in chloroform) (Found : C, 67·8, 67·5 ; H, 5·2, 5·5 ; mol. wt., 334, 340, 361 ; $\lambda_{max.}$ 235 mμ ; log $\varepsilon_{max.}$ 3·97 ; $\lambda_{max.}$ 288 mμ ; log $\varepsilon_{max.}$ 3·92 ; calculated from acceptable values of optical density. Calc. for $C_{20}H_{18}O_6$: C, 67·8 ; H, 5·1% ; mol. wt., 354).

It gave a strong red colour with conc. sulphuric acid, a strong brownish yellow colour with tetranitromethane, failed to decolorize bromine, gave a negative test for primary and secondary hydroxyl groups (Fearon and Mitchell 1932), contained no methoxyl groups, and could not be acetylated. For (+)-asarinin, Huang-Minlon (1937) records m.p. 121–122 °C and $[\alpha]_D^{18}$ +121·7° in chloroform.

Material from the crude benzene extract once recrystallized from ethanol gave $[\alpha]_D^{28}$ +117±1° (*c*, 3·4 in chloroform) indicating that asarinin was not accompanied by (—)-asarinin or sesamin.

(*b*) *Isomerization to Sesamin.*—(+)-Asarinin (5 g), conc. hydrochloric acid (50 ml), and ethanol (450 ml) were refluxed together for 16 hr. By refrigeration, 2·12 g of unchanged material were recovered. The concentrated mother liquor yielded a further 1·99 g of material which was recrystallized from ethanol to m.p. 121–122 °C, $[\alpha]_D^{26·5}$ +67±1° (*c*, 0·7 in chloroform), mixed m.p. with (+)-asarinin 98–105 °C. Huang-Minlon (1937) finds m.p. 121–122°, $[\alpha]_D^{18}$

$-68{\cdot}9°$ (in chloroform) for (—)-sesamin, and Kaku, Kutami, and Takahashi (1936), m.p. 123–124 °C, $[\alpha]_D^{19}$ $+68{\cdot}1°$ (in chloroform) for (+)-sesamin.

(*c*) *Dinitroasarinin.*—Asarinin was nitrated below 45 °C in glacial acetic acid with conc. nitric acid. Dinitroasarinin was precipitated with water, filtered, and recrystallized from dioxane and finally glacial acetic acid to constant m.p. 224·0–226·5 °C, $[\alpha]_D^{27}$ $-25\pm1°$ (*c*, 4·7 in chloroform). Kaku, Kutami, and Takahashi (1936) record m.p. 220–221 °C, $[\alpha]_D^{17}$ $-29{\cdot}5°$ (Found: C, 54·2; H, 3·6%. Calc. for $C_{20}H_{16}O_{10}N_2$: C, 54·0; H, 3·6%).

(*d*) *4-Nitro-1,2-Methylenedioxybenzene.*—Asarinin (2 g) dissolved in glacial acetic acid and conc. nitric acid (5 ml) was heated on a water-bath. Dinitroasarinin (0·68 g) was filtered off, and water was added to the filtrate, precipitating 0·8 g of 4-nitro-1,2-methylenedioxybenzene. Crystallization from ethanol and from acetone yielded yellow needles, m.p. 147–148 °C. Huang-Minlon (1937) records m.p. 146–147 °C (Found: C, 50·1; H, 3·2%. Calc. for $C_7H_5O_4N$: C, 50·3; H, 3·0%).

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THE ACTION OF UNSATURATED ALDEHYDES ON WOOL

By J. R. McPhee* and M. Lipson*

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Summary

The action on wool of acraldehyde α-methacraldehyde, crotonaldehyde, and cinnamaldehyde has been studied. Of these compounds, acraldehyde reacts most readily, combining with the free sulphydryl groups and reacting under alkaline conditions with the lysine. There is no evidence from physical measurements to suggest the presence of new cross-links. Reaction becomes much more marked on reduction of the wool, both carbonyl and olefinic groupings of the acraldehyde derivatives reacting with cysteine residues. Acraldehyde also reacts with the lysine in reduced wool. Physical measurements on reduced wool treated with acraldehyde or α-methacraldehyde indicate that cross-linking has occurred.

I. Introduction

The incorporation of new cross-linkages between the peptide chains of wool has received considerable attention as a means of improving the mechanical properties of the fibre and increasing its resistance to certain types of chemical and biological degradation. Reagents such as formaldehyde (Speakman and Peill 1943), mercuric acetate (Speakman and Coke 1939), and benzoquinone (Meunier 1911) have been recommended to enhance mechanical properties, whilst formaldehyde is also claimed to improve alkali resistance (Kann 1914) and to prevent moth attack (Traill and McLean 1942); mercuric acetate can also mothproof wool (Lipson, unpublished data). Carboxylic and basic side-chains are considered to be the main groups involved in such reactions although, under certain conditions, tyrosine (Alexander, Carter, and Johnson 1951) and cystine (Middlebrook and Phillips 1942) may react. New types of cross-linkages have also been formed by reducing the disulphide bonds in wool to sulphydryl side-chains which are then reacted with metallic salts or alkylene dihalides (Speakman 1936*b*). Wool treated by the latter method shows increased resistance to alkali and is mothproof (Geiger, Kobayashi, and Harris 1942).

The present investigations were undertaken to examine the action on wool of αβ-unsaturated aldehydes, such as acraldehyde, where the difunctional structure would allow of several theoretical possibilities of cross-linking.

The literature contains few references to the action of such compounds on wool and other proteins. Gustavson (1940) has shown that acraldehyde and crotonaldehyde react to a certain extent with free amino-groups in collagen.

* Wool Textile Research Laboratory, C.S.I.R.O., Geelong, Victoria.

Jones, Thorsen, and Lundgren (1952) reacted acraldehyde with wool and considered that combination with amino- or imino-groups occurred as follows:

$$>NH+CH_2=CH.CHO\rightarrow>N.CHOH.CH=CH_2.$$

The free ethylenic double bonds were then used to form new disulphide cross-linkages by reaction with sulphur monochloride.

Acraldehyde and other αβ-unsaturated aldehydes are known to react readily with thiol compounds (Gresham and Schweitzer 1949; Vinton 1949) according to the following general scheme:

$$R.CH_2SH+R'(R'')C:C(R''').CHO\rightarrow R.CH_2.S.R'(R'')C.CH(R''').CHO.$$

A preliminary experiment in the present investigations showed that acraldehyde reacted instantaneously in the cold with the thiol groups of cysteine. It seemed likely, therefore, that reaction would take place with thiol groups in reduced wool. Consequently, new cross-linkages might be possible between >NH and −SH groups in reduced wool by reaction with the carbonyl grouping and double bond respectively of an αβ-unsaturated aldehyde.

The present investigations were undertaken to study this possibility and, at the same time, to observe the effects of the treatments on alkali resistance and moth attack.

II. Experimental

(a) *Materials*

(i) *Loose Wool.*—The base portion of a 56's Crossbred fleece was purified by Soxhlet extraction with light petroleum (8 hr) and ethanol (6 hr) followed by five successive washings with distilled water at 50 °C.

Samples of this loose wool were used for work of a fundamental nature, single fibres being taken for elasticity and supercontraction measurements.

(ii) *Fabric.*—The wool consisted of scoured plain-weave fabric made from 64's Merino wool and had the following construction: warp yarn, 33's Yorkshire skeins; weft yarn, 30's Yorkshire skeins; 32 ends/in; 30 picks/in. It was purified in the same manner as the loose wool.

(iii) *Nylon Yarn.*—Waste nylon yarn was purified by washing several times in soap solution at 80 °C to remove size before extraction as above.

(iv) *αβ-Unsaturated Aldehydes.*—Acraldehyde, α-methacraldehyde, crotonaldehyde, and cinnamaldehyde were pure stabilized samples freshly distilled before use to remove the stabilizer, usually hydroquinone.

(b) *Methods*

(i) *Treatment with αβ-Unsaturated Aldehydes.*—The loose wool was treated with 60 times its weight of a buffer solution of the reagent with initial wetting out *in vacuo*. A liquor : wool ratio of 30 : 1 was used with fabrics. After treatment, the wool was washed in several changes of distilled water over a period of 2 days.

The reactions were followed by finding the increase in weight on treatment with different reagents. Fabric samples were conditioned for 24 hr at 22 °C and 65 per cent. R.H. before weighing while loose wool was dried for 2 hr *in vacuo* at 105 °C.

(ii) *Thiol and Disulphide Sulphur Estimations.*—The wool was hydrolysed by refluxing for 4 hr in hydrochloric acid (5N), thiol and disulphide sulphur being determined colorimetrically

by the technique of Shinohara (1935, 1936*a*, 1936*b*) using a Spekker absorptiometer. The sulphur contents were calculated on the original dry weight of wool.

(iii) *Acetylation of Wool.*—The $-NH_2$ groups were acetylated by the I. G. Farben process reported by Evans (1949). This consisted in treating a 1 g sample of loose wool for 4 hr at 60 °C in a solution containing acetic anhydride (7·7 ml), glacial acetic acid (43·0 ml), concentrated sulphuric acid (0·03 ml), and pyridine (0·3 ml). The acetylated wool was washed in several changes of distilled water and dried. Acetylation produced weight increases of 7–8 per cent.

It has been shown (Alexander, Carter, and Johnson 1951) that 75–80 per cent. of the amino-groups are blocked by this procedure, but it is not known to what extent other groups are affected.

(iv) *Alkali Solubility.*—Samples to be tested were dried for 2 hr *in vacuo* at 105 °C and treated in sodium hydroxide solution (0·1N ; 100 ml/g dry wool) at 65 °C for 1 hr and washed with 2 l. of distilled water on a Buchner funnel. The percentage loss in weight of the samples represents the alkali solubility (Harris and Smith 1936).

(v) *Chromatography.*—Samples were hydrolysed by refluxing overnight in hydrochloric acid (6N) and analysed qualitatively by the technique of Consden, Gordon, and Martin (1944), using phenol and butanol-acetic acid as solvents.

(vi) *Supercontraction.*—Single fibres, fitted in setting frames, were relaxed in cold water and measured ; they were then treated for 30 min at 100 °C in a solution of sodium bisulphite (5% ; w/v) (Speakman 1936*a*). After washing in running water for 2 hr, the fibres were dried and again measured.

(vii) *Work Required to Stretch Fibres 30 Percent.*—Fibres were stretched in water at 22 °C to 30 per cent. of their original length on a Cambridge extensometer both before and after treatment. From the areas under the stress-strain curves, the change in the work required to produce a 30 per cent. increase in length (30% index) was determined (Speakman 1947).

(viii) *Reduction of Wool.*—The wool was reduced in 60 times its weight of thioglycollic acid (0·2M), brought to pH 4·5 with potassium hydroxide. Reduction was allowed to proceed for 18 hr at 22 °C before the samples were rinsed in distilled water (3 times), ethanol (3 washes of 30 min each), and finally washed in several changes of distilled water for a day.

(ix) *Determination of —CHO Groups in Wool.*—The method of Cuthbertson and Phillips (1945) was used. Potassium acetate (8 g) in methanol (30 ml) was added to semicarbazide hydrochloride (8 g) in water (20 ml) ; the solution was filtered and the filtrate made up to 400 ml with water. Wool (1 g) was heated at 40 °C for 23 hr with 60 ml of this semicarbazide solution (60 ml), then rinsed with water several times daily for 8 days. Reactivity was determined from the weight increase.

III. Reaction with Normal Wool

Preliminary experiments using acraldehyde under various conditions showed that treatment substantially lowered the alkali solubility of the wool. The results are summarized in Table 1.

It is seen that the alkali solubility is not directly related to weight increase. Values for the latter continue to rise with increasing concentration, pH, time, and temperature, due, no doubt, to polymerization of excess acraldehyde.

From these experiments, the following standard conditions were selected for future treatments : 0·5 per cent. by volume acraldehyde at pH 8·0 (0·2M phosphate) temperature 50 °C for 6 hr.

Experiments were next carried out comparing acraldehyde with other αβ-unsaturated aldehydes in equimolar concentrations under the above standard conditions. Acetaldehyde and acrylonitrile were included to assess separately the respective effects of an aldehyde grouping and a double bond. The results are shown in Table 2.

Acraldehyde reacted to a much greater extent than the other compounds and decreased alkali solubility the most. All compounds excepting acrylonitrile reduce alkali solubility by varying amounts.

The analytical values show that acraldehyde reacted with practically all the free cysteine (0·025 m mole/g) but not with the cystine in the wool; the

TABLE 1

REACTION OF ACRALDEHYDE WITH WOOL

Concentration (%, v/v)	pH	Temperature (°C)	Time (hr)	Weight Increase* (%)	Alkali Solubility (%)
0·1	8·0	50	18	2·7	2·0
0·3	8·0	50	18	3·8	1·3
0·5	8·0	50	18	4·3	1·6
1·0	8·0	50	18	5·3	1·3
2·0	8·0	50	18	6·6	1·5
3·0	8·0	50	18	8·1	1·7
5·0	8·0	50	18	11·3	2·5
0·5	0·9	50	18	0·9	3·2
0·5	3·0	50	18	2·5	3·1
0·5	3·8	50	18	3·0	2·1
0·5	6·0	50	18	3·3	2·3
0·5	7·9	50	18	4·6	2·0
0·5	9·8	50	18	5·0	2·2
0·5	10·8	50	18	8·2	1·7
0·5	8·0	25	18	3·4	2·4
0·5	8·0	35	18	3·9	2·2
0·5	8·0	50	18	4·5	2·0
0·5	8·0	65	18	5·7	2·0
0·5	8·0	85	18	10·2	1·6
0·5	8·0	50	0·5	2·1	2·9
0·5	8·0	50	1·0	2·6	2·7
0·5	8·0	50	2·0	3·1	2·9
0·5	8·0	50	4·0	3·3	2·5
0·5	8·0	50	6·0	3·9	2·2
0·5	8·0	50	18	4·3	2·2
0·5	8·0	50	30	4·8	2·2
Untreated	—	—	—	—	5·8

* Weight increases of treated samples have been corrected according to weight alterations of controls treated in buffer only.

other compounds cause no significant changes in either cysteine or cystine contents. From the analytical results, it can be seen that the amount of acraldehyde combined is considerably in excess of cysteine reacted.

Experiments were next undertaken to ascertain whether, besides sulphydryl, amino- or imino-groups had reacted.

Samples of loose wool were treated with acraldehyde at pH values of 1, 8, and 11. The treated wool was hydrolysed and analysed qualitatively by means of filter paper chromatography. No lysine spot was obtained from the hydrolysates of wool which had been treated with acraldehyde at pH 8 or 11, although all the amino acids were present if the treatment had been carried out at pH 1. All the usual amino acids were found to be present in hydrolysates of wool treated with the other compounds.

Acraldehyde has, therefore, reacted with lysine side-chains probably through the carbonyl group as suggested by Jones, Thorsen, and Lundgren (1952). In support of this, it was found that acetylation of wool, which would block basic groups, considerably diminished subsequent reaction with acraldehyde. Acetylated wool, when treated under standard conditions, showed an increase in weight of only 0·6 per cent. It is apparent, therefore, that reaction with lysine has accounted for most of the weight increase with acraldehyde.

TABLE 2

REACTION OF UNSATURATED ALDEHYDES WITH WOOL

Compound	Weight Increase (%)	Aldehyde Reacted (m mole/g dry wool)	Alkali Solubility (%)	Cysteine (%)	Cystine (%)
Acraldehyde	3·3	0·58	2·5	0	13·2
α-Methacraldehyde ..	1·9	0·27	4·1	0·3	13·2
Crotonaldehyde ..	1·5	0·22	3·3	0·2	13·1
Cinnamaldehyde ..	0·5	0·04	4·7	0·3	13·2
Acetaldehyde	0·3	0·06	4·5	0·3	13·3
Acrylonitrile	0·7	0·12	6·9	0·2	13·4
Control (buffer only) ..	—	—	5·8	0·3	13·2

Indirect evidence, that imino-groups of the main chain are not involved to any great extent, was obtained by treating nylon with acraldehyde. When nylon yarn was treated under optimum conditions, only a very slight increase in weight resulted, indicating that reaction with the peptide groups in wool could only be slight.

(*a*) *Some Properties of Treated Wool*

(i) *Stability to Acid.*—Brown, Hornstein, and Harris (1951) have shown that the increased resistance to alkali conferred on wool by formaldehyde treatment is removed on boiling with acids. This is not the case when wool is treated with acraldehyde. Treated samples were refluxed for 1 hr with hydrochloric acid (0·1N) and thoroughly washed in running water. Alkali solubilities of samples before and after acid treatment are given in Table 3.

These results show that the new linkages formed in wool from treatments with acraldehyde at pH 8 and 11 are stable to acid. However, the linkages formed at pH 1 are less stable to acid boiling.

TABLE 3

ALKALI SOLUBILITIES OF TREATED WOOL

pH		Alkali Solubility (%)	
		Treated Wool	Controls (buffer only)
1	Before acid boiling	3·6	7·0
	After acid boiling	5·8	15·9
8	Before acid boiling	2·6	5·2
	After acid boiling	2·7	11·1
11	Before acid boiling	1·5	1·6
	After acid boiling	1·6	4·2

(ii) *Presence of Free Aldehyde Groups.*—The presence of free aldehyde groups in treated wool can be shown by reaction with semicarbazide.

Loose wool was treated with acraldehyde, α-methacraldehyde, and crotonaldehyde at pH 8·0 under the conditions previously used. After weight increases had been determined, the samples were treated with semicarbazide. Wool which had been treated with acraldehyde reacted appreciably, that treated with α-methacraldehyde reacted only about half as much, whilst wool treated with crotonaldehyde reacted to an even smaller extent (Table 4).

TABLE 4

PRESENCE OF ALDEHYDE GROUPINGS IN TREATED WOOL

Treatment	Aldehyde Reacted (m mole/g dry wool)*	Semicarbazide Reacted (m mole/g dry wool)*
Untreated	—	0
Buffer only	—	0
Acraldehyde	0·62	0·13
α-Methacraldehyde	0·24	0·06
Crotonaldehyde	0·22	0·03

* Calculated from weight increase.

Since untreated wool shows no reaction with semicarbazide, the unsaturated aldehydes must introduce free carbonyl groups into the wool by reaction via their ethylenic double bonds. The fact that combined aldehyde is considerably in excess of reacted semicarbazide indicates that carbonyl groups of the aldehyde have been used up in reaction with the wool.

(iii) *Supercontraction and Elastic Properties.*—Treatment with acraldehyde does not alter the amount of supercontraction caused by boiling sodium bisulphite. There is, however, approximately 50 per cent. reduction in the supercontraction caused by lithium bromide. No significant alterations were observed in 30 per cent. indices of single fibres in water before and after treatment. These results indicate that any cross-linking that may have occurred during treatment is insufficient to cause major changes in the mechanical properties of the fibre.

IV. Reaction with Reduced Wool

Table 5 records the experimental results obtained by treating reduced wool with the various compounds under the standard conditions described earlier.

Much larger weight increases have occurred with reduced wool than with normal wool. Treatment with acraldehyde substantially decreases the alkali solubility of the wool; α-methacraldehyde and crotonaldehyde cause similar but less marked effects. Acrylonitrile and acraldehyde show most reaction

Table 5

REACTION OF UNSATURATED ALDEHYDES WITH REDUCED WOOL

Compound	Weight Increase (%)	Aldehydes Reacted (m mole/g dry wool)	Alkali Solubility (%)	Cysteine Reacted (m mole/g dry wool)*
Acraldehyde	7·5	1·33	1·5	0·22
α-Methacraldehyde	6·5	1·07	3·8	0·14
Crotonaldehyde	5·2	0·91	3·6	0·08
Cinnamaldehyde	5·4	0·41	6·0	0·09
Acetaldehyde	2·0	0·37	7·8	—
Acrylonitrile	3·6	0·68	15·2	0·61
Reduced and treated in buffer only	—0·4	—	14·9	—
Untreated	—	—	5·9	—

* These values represent the difference between free cysteine in hydrolysates of control and treated wools and hence the amounts of cysteine which have reacted to form linkages stable to hydrolysis.

with cysteine in forming bonds stable to acid hydrolysis. The average cysteine content of reduced controls was found to be 0·53 m mole/g dry wool. The amount of cysteine available for reaction was no doubt slightly higher than this, but some has probably oxidized to cystine during hydrolysis prior to analysis.

(*a*) *Some Properties of Treated Wool*

(i) *Supercontraction in Sodium Bisulphite.*—Supercontraction in boiling bisulphite of reduced fibres treated with acraldehyde at pH 1, 8, and 11 is given in Table 6, each value representing the mean of at least three determinations.

Table 6

SUPERCONTRACTION OF TREATED FIBRES IN SODIUM BISULPHITE

pH	Control (buffer only)	Supercontraction (%)	
		Untreated	Treated
1·2	22		1
7·8	33		—1
10·8	0		0
Untreated		31	

The fibres treated with acraldehyde at all pH values do not supercontract.

Supercontraction of fibres treated at pH 8·0 with the series of six compounds is given in Table 7. It is seen that treatment with acraldehyde or α-methacraldehyde practically eliminates supercontraction of reduced wool in boiling sodium bisulphite. Crotonaldehyde is only partially effective, whilst the other compounds are without significant effect.

TABLE 7

SUPERCONTRACTION OF TREATED FIBRES IN SODIUM BISULPHITE

Fibre	Supercontraction (%)
Untreated	25
Control (reduced and treated in buffer)	25
Acraldehyde treated after reduction	2
α-Methacraldehyde after reduction	2
Crotonaldehyde " "	14
Cinnamaldehyde " "	26
Acetaldehyde " "	25
Acrylonitrile " "	20

(ii) *Elastic Properties.*—The 30 per cent. index of reduced fibres is increased by treatment with acraldehyde or α-methacraldehyde at pH 8·0 but there is apparently insufficient cross-linking to restore it to that of unreduced wool. The values given in Table 8 represent the mean of six fibres in each treatment.

(iii) *Swelling in Trichloroacetic Acid.*—The swelling in trichloroacetic acid (5N) of reduced wool treated with acraldehyde was compared with that of reduced controls treated in buffer only. Treated fibres gave a mean value of 17 per cent. diameter increase as against 27 per cent. for the reduced controls.

TABLE 8

EFFECT OF TREATMENTS ON ELASTIC PROPERTIES

Treatment	30 Per cent. Index (%)
Reduction alone	—21·0
Reduction followed by acraldehyde	—10·0
Reduction followed by α-methacraldehyde	—11·5

(iv) *Resistance to Moth Attack.*—Reduced wool treated with either acraldehyde or α-methacraldehyde shows very good resistance to moth attack. α-Methacraldehyde efficiently proofs wool with treatments in the pH range 1 to 8, the effect diminishing above pH 8. Acraldehyde treatment is most effective under alkaline conditions, the efficiency decreasing below pH 6. Details of these experiments will be reported elsewhere.

V. Discussion

Acetaldehyde, acrylonitrile, and cinnamaldehyde show little reaction with normal wool. Any percentage changes in cystine and cysteine are negligible, whilst filter paper chromatography reveals no differences between treated samples and untreated controls. Crotonaldehyde and α-methacraldehyde show some reaction which is, however, insufficient to cause detectable changes in amino acid composition.

Acraldehyde is by far the most reactive compound, combining with most of the free sulphydryl groups in the wool and reacting under alkaline conditions with the lysine ; reaction with disulphide bonds was not detected. The following reactions probably take place :

$$\underset{\text{(lysine side-chain)}}{-CH_2-NH_2} + CH_2=CH.CHO- \rightarrow -CH_2.NH.CHOH.CH=CH_2,$$

$$\underset{\text{(cysteine side-chain)}}{-CH_2.SH} + CH_2=CH.CHO- \rightarrow -CH_2.S.CH_2.CH_2.CHO.$$

These suggested reactions are supported by the absence of lysine and cysteine and the presence of free aldehyde groups in wool after treatment.

There are two possible reasons for the decreased alkali solubility of normal wool after acraldehyde treatment. Firstly, new alkali resistant cross-linkages could have been formed through the same molecule of acraldehyde reacting with lysine and cysteine according to the above equations. Secondly, certain existing disulphide bonds could have been rendered less labile and more alkali resistant through steric effects resulting from the reaction. Any cross-linking that may have occurred has been insufficient to be detected by physical measurements. The effect on alkali resistance could be explained by reaction of acraldehyde with $-NH_2$ groups situated close to disulphide bonds. Lindley and Phillips (1947) and Cecil (1950) consider that the reactivity of $-S-S-$ groups can be influenced by neighbouring $-NH_2$ groups. Blocking the latter by substitution can decrease the lability of the former. Thus, the greater stability to alkali resulting from acraldehyde treatment could have been produced by reaction with $-NH_2$ groups situated near labile $-S-S-$ groups.

Comparing Tables 2 and 5, it is seen that reduced wool reacts much more readily with all compounds. Acrylonitrile has shown the greatest reactivity with $-SH$ groups. The reaction is undoubtedly double bond addition, which is supported by the fact that the amount of acrylonitrile combined per gram of wool is chemically equivalent to the difference in total cystine plus cysteine between treated sample and reduced control (Table 5).

Acetaldehyde has probably reacted with cysteine in reduced wool to form the hemimercaptal. There is, however, no decrease in SH content of the hydrolysate, indicating that the bonds formed are split during hydrolysis. There may have been reaction with basic side-chains although this has not been shown in the present experiments.

The unsaturated aldehydes all give rise to greater weight increases than the above two compounds. In each instance, cysteine has probably combined both with carbonyl groupings and olefinic double bonds. The last column in Table 5 would indicate the extent of reaction with olefinic double bonds. It is seen that acraldehyde is the most reactive in this regard.

There is reasonable evidence to show that acraldehyde has introduced new cross-linkages in reduced wool. Physical data such as elimination of super-contraction in bisulphite, alterations in elastic properties, and decreased swelling in trichloroacetic acid all support this view. The results cannot be explained in simple terms and would depend on the spatial arrangement of thiol and other functional groups after reduction. Either or both of the following cross-linking reactions might occur with acraldehyde:

$$\underset{\text{(cysteine)}}{\text{—CH}_2\text{—SH}} + \text{CH}_2\text{=CH.CHO} + \underset{\text{(cysteine)}}{\text{HS—CH}_2\text{—}} \rightarrow \text{—CH}_2\text{.S.CH}_2\text{.CH}_2\text{CHOH—S—CH}_2\text{—}$$

$$\underset{\text{(lysine)}}{\text{—CH}_2\text{.NH}_2} + \text{CH}_2\text{=CH.CHO} + \underset{\text{(cysteine)}}{\text{HS.CH}_2\text{—}} \rightarrow \text{—CH}_2\text{.NH.CHOH.CH}_2\text{.CH}_2\text{.S.CH}_2\text{—}$$

With α-methacraldehyde the second possibility would not exist due to the fact that there is no detectable alteration in lysine content after treatment.

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SHORT COMMUNICATIONS

THE FORCES BETWEEN CENTRO-SYMMETRIC MOLECULES*

By J. S. Rowlinson†

The thermodynamic properties of fluids composed of molecules of the type XY_4 and XY_6 may be compared with those of the inert gases by means of the principle of corresponding states. The main differences are: (i) the reduced second virial coefficients are larger than those of the inert gases at high temperatures and smaller at low temperatures, (ii) the ratio pV/RT at the critical point is lower for the centro-symmetric molecules, (iii) their reduced vapour pressures change more rapidly with temperature and so their Trouton constants are larger, (iv) the reduced densities of the liquids are higher, and (v) the heat capacities of the liquids at constant volume are larger.

These differences must be due to differences in the forms of the intermolecular potentials. Recently two modifications of the inert gas potentials have been suggested as the cause of these differences. Hamann and Lambert (1954*a*, 1954*b*) have suggested potentials similar to those of the inert gases, in that they are spherically symmetrical, but the greater part of whose origin lies not at the centre of the molecule but evenly distributed over the surface of a sphere whose radius is the $X-Y$ bond length. Following the method of Thomaes (1952), they have calculated the probable form of the total potential for this model and such of the properties as are susceptible to *a priori* calculation. They are able to show good agreement for the second virial coefficient and, subject to the unavoidable crudity of the statistical treatment, qualitative agreement for the second and third of the properties above.

However, the same differences can be accounted for quite as convincingly by assuming that the molecules have a central force-field similar to that of the inert gases and also a non-central force-field whose average over all orientations is zero. The non-central forces are treated as a perturbation of a central force assembly (Cook and Rowlinson 1953; Rowlinson 1954). It is the object of this note, firstly, to suggest how it is that two so dissimilar models can account for the same facts and, secondly, to review the evidence to see if a decision can be made between them.

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† Department of Chemistry, University of Manchester.

The similarity between the two treatments is best brought out by regarding them both as the introduction of perturbing potentials into an assembly of molecules with the (12,6) inverse-power potential usually used for the inert gases. The perturbation is " radial " in the first case and " orientational " in the second. A potential similar to that of Hamann and Lambert can be obtained by superimposing on the (12,6) potential between molecules i and j, W^0_{ij}, an additional radial potential W^1_{ij} of the form shown in Figure 1. The exact form of W^1_{ij} is immaterial as long as

$$\int_0^\infty W^1_{ij}.4\pi r^2_{ij}\mathrm{d}r_{ij}=0. \qquad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

The total potential $(W^0_{ij}+W^1_{ij})$ is sixth power at very large distances, but has a deeper and narrower trough than the (12,6) potential and, at least for low energy collisions, a steeper repulsive potential. Consider now an assembly of N

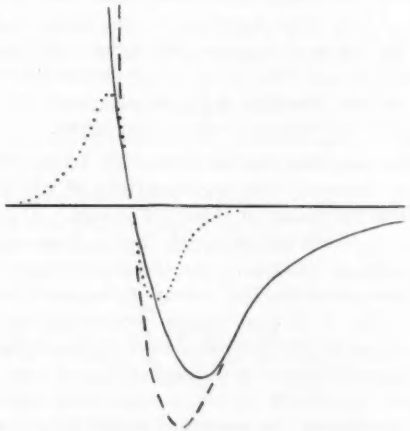

Fig. 1.—The intermolecular potentials (schematic).

—— W^0_{ij}.

···· W^1_{ij}.

---- $(W^0_{ij}+W^1_{ij})$.

molecules whose total intermolecular energy U can be written as the sum of two terms, U^0 due to the potentials W^0_{ij}, and U^1 due to the perturbing potentials W^1_{ij}. Following Pople's (1954*a*, 1954*b*) treatment of the orientational case, the free-energy of the assembly,

$$F=-kT\ln[\int..\int \mathrm{e}^{-U/kT}\mathrm{d}\tau], \qquad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

can be written as a Taylor series whose first term F^0 is the free-energy of an assembly of intermolecular energy U^0 and whose second term is

$$F^1 = \int..\int U^1 e^{-U^0/kT} d\tau / \int..\int e^{-U^0/kT} d\tau \quad \ldots\ldots\ldots (3)$$

$$= \overline{U^1} \quad \ldots\ldots\ldots (4)$$

$$= \tfrac{1}{2} \overline{\sum_{i,j} W^1_{ij}} \quad \ldots\ldots\ldots (5)$$

$$= \tfrac{1}{2} V \int_0^\infty n^0_2(r_{ij}) W^1_{ij} . 4\pi r^2_{ij} dr_{ij}, \quad \ldots\ldots\ldots (6)$$

where the bar denotes a statistical average and where $n^0_2(r)$ is the pair distribution function of the unperturbed assembly. Unfortunately, $n^0_2(r)$ cannot yet be calculated with any accuracy, except at low densities where

$$n^0_2(r_{ij}) = (N/V)^2 e^{-W^0_{ij}/kT} \quad \ldots\ldots\ldots (7)$$

$$\simeq (N/V)^2 (1 - W^0_{ij}/kT). \quad \ldots\ldots\ldots (8)$$

This last step is permissible as a first approximation, as W^1_{ij} is greatest where W^0_{ij} is small. Although (7) and (8) are valid only at low densities, experimental determinations of $n^0_2(r)$ in liquid argon show that it behaves similarly to (8) at distances close to the collision diameter. So, for the purposes of this note, (8) may be taken as an adequate representation of $n^0_2(r)$. Substituting in (6),

$$F^1 = -\frac{N}{2kT} \int_0^\infty W^0_{ij} W^1_{ij} . \frac{4\pi N r^2_{ij} dr_{ij}}{V}. \quad \ldots\ldots\ldots (9)$$

The integral is positive, and so it is seen that the radial perturbation W^1_{ij} decreases the free-energy by an amount which varies as $1/kT$ and whose magnitude increases with increasing density. These are just the properties of the free-energy difference caused by certain kinds of orientational perturbations (cf. eqn. (1.9), Rowlinson 1954). The other differences in equilibrium properties can be derived by differentiating the free-energy and so it is clear how these treatments lead to such similar results. Experimentally there is, for example, a great similarity between the reduced properties of SF_6 and CO_2. In the latter orientational forces are undoubtedly present.

It is unlikely, therefore, that further consideration of these differences will decide between the two explanations. The treatment of Hamann and Lambert seems, at first sight, the more reasonable for such molecules, and probably this radial perturbation is important. However, there is indirect evidence that the potentials also vary with orientation. Consider the pairs SF_6—SF_6 and UF_6—UF_6. The treatment of Hamann and Lambert would suggest that the forces in the second case, arising to a large extent from the electron shells of

the U atom, would be more like those of the inert gases than those in the first case. However, the experimental results show that UF_6 shows the greater deviations from the inert gases. Similar considerations apply to the pairs CCl_4 and CF_4. This behaviour is more understandable if orientational forces are admitted. The strong attraction of the two U atoms will bring the F atoms so close that they must be strongly repelling each other. The total energy will then vary with the F—F distances and so with the orientations of the U—F bonds in the two molecules. The heavier the central atom, the greater is this effect. This is confirmed by the densities of the solid SF_6 and UF_6 which, if the molecules were spherical, would require F—F distances of 1·9 and 1·5 Å respectively. At such separations the F atoms must repel strongly as may be seen by comparing these distances with the equilibrium separation of two Ne atoms of 3·1 Å. In fact, in solid UF_6 the orientational forces are strong enough to destroy the octahedral symmetry of the molecules and the structure is determined mainly by the packing of the F atoms (see Katz and Rabinowitch 1951).

In short, the surprisingly large deviations of centro-symmetric molecules from the behaviour shown by the inert gas molecules are probably due to differences both in the radial and orientational components of the intermolecular potential.

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THE DISSOCIATION CONSTANT OF METHYLENE GLYCOL (FORMALDEHYDE HYDRATE)*

By R. J. L. Martin†

There is strong evidence that aqueous solutions of formaldehyde are almost entirely solutions of methylene glycol and its polymers. This has been reviewed by Walker (1953, p. 46):

$$CH_2{=}O + H_2O \rightleftharpoons CH_2(OH)_2.$$

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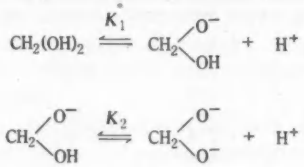
† Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

Methylene glycol is a weak acid and can ionize in the following way :



The first dissociation constant of methylene glycol has been measured by various workers and their results are given in Table 1. It will be noted that they are not entirely in agreement because there is an irregular change in dissociation constant with temperature. Since a reliable value for the dissociation constant was required for other work it was necessary to determine it at 40 °C.

TABLE 1

DISSOCIATION CONSTANT OF METHYLENE GLYCOL

Temperature (°C)	Dissociation Constant (g-mol l^{-1})	Reference
0	$1{\cdot}0 \times 10^{-14}$	Euler and Euler (1905)
15	$1{\cdot}2 \times 10^{-13}$	Sauterey (1949)
20	$0{\cdot}4 \times 10^{-13}$	Veselý and Brdička (1947)
23	$1{\cdot}62 \times 10^{-13}$	Wadano (1934)
30	$1{\cdot}35 \times 10^{-13}$	Levy (1934)
50	$3{\cdot}3 \times 10^{-13}$	Euler and Lövgren (1925)

It was found that the cell,

$$\text{Pt black} \mid H_2(g) \mid CH_2O,\ NaOH,\ NaCl \mid AgCl(s) \mid Ag,$$

which involves no liquid junction, was unsatisfactory for the determination, because the silver chloride electrode was reduced to silver by the alkaline formaldehyde.

The measurements were made with the cell,

$$Hg \mid HgCl(s) \mid NaCl \mid CH_2O,\ NaOH,\ NaCl \mid H_2(g) \mid \text{Pt black},$$

which eliminates any reducing action of the alkaline formaldehyde by means of a liquid junction. The results obtained are given in Table 2 and show that although there are variations in the dissociation constant, there is a tendency for it to increase with increasing alkali concentration.

The Cannizzaro reaction of the formaldehyde has been reduced to a negligible amount by using low concentrations of formaldehyde and alkali. In confirmation of this, the analysis of the cell liquid did not indicate a detectable change in the formaldehyde concentration after a determination.

TABLE 2

DISSOCIATION CONSTANT OF METHYLENE GLYCOL AT 40 °C

NaOH = a (g-mol l^{-1})	$CH_2O = b$ (g-mol l^{-1})	b/a	K_h* (g-mol l^{-1})	$OH^-_{obs.}$ (g-mol l^{-1})	$K_1^* \times 10^{-13}$ (g-mol l^{-1})
0·0527	0·00953	0·181	0·125	0·0499	2·17
0·0527	0·0144	0·273	0·110	0·0482	2·46
0·0527	0·0241	0·458	0·117	0·0458	2·32
0·0264	0·0481	1·818	0·129	0·0200	2·10
0·0209	0·0481	2·301	0·137	0·0159	1·98
0·0158	0·0481	3·048	0·162	0·0124	1·67
0·0209	0·0718	3·439	0·160	0·0148	1·69
			Mean 0·134		Mean $2·06 \times 10^{-13}$

* K_h, hydrolysis constant; K_1, dissociation constant.

The change in the dissociation constant may be due to the second dissociation being larger than expected.

Since

$$[OH^-] + \left[CH_2(O^-)(OH)\right] + 2\left[CH_2(O^-)_2\right] = a,$$

$$[CH_2(OH)_2] + \left[CH_2(O^-)(OH)\right] + \left[CH_2(O^-)_2\right] = b,$$

and

$$K_h = [CH_2(OH)_2]\,[OH^-] \Big/ \left[CH_2(O^-)(OH)\right], \quad \ldots\ldots\ldots \quad (1)$$

$$K'_h = \left[CH_2(O^-)(OH)\right][OH^-] \Big/ \left[CH_2(O^-)_2\right],$$

it follows that

$$\{K_hK'_h[OH^-]^2 + K_h[OH^-] + 1\}(a - [OH^-]) = b\{2K_hK'_h[OH^-]^2 + K_h[OH^-]\}. \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

In this expression a and b are the total alkali and formaldehyde concentrations respectively and K_h and K'_h are the first and second hydrolysis constants respectively.

The method of least squares was used to calculate the coefficients of an assumed linear relationship between K_1 and b/a. From two values of K_1 for

widely separated values of b/a, the actual hydroxyl ion concentration was obtained from equation (**1**) by back calculation. The two sets of values for a, b, and the hydroxyl ion concentration were substituted in equation (**2**) and the simultaneous equations solved for K_h and K'_h. K_h and K'_h were found to be 0·18 and 0·20 g-mol l^{-1} respectively, thus making K_1 and K_2, $1{\cdot}5\times10^{-13}$ and $1{\cdot}4\times10^{-13}$ respectively.

Phosphoric, carbonic, and sulphurous acids have adjacent hydroxyl groups as in methylene glycol and possess a second dissociation constant smaller than the first by a factor of at least 10^3. Methylene glycol would be expected to have a similar relationship between the first and second dissociation constants. It follows that the data are not sufficiently accurate to assess the second dissociation constant and are only capable of giving the first dissociation constant approximately.

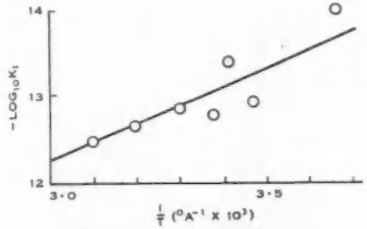


Fig. 1.—Graph of $\log_{10} K_1$ against $1/T$ for all determinations of the dissociation constant of methylene glycol.

The accuracy of the determination was reduced because the junction potential varied in spite of attempts to keep it as constant as possible. With the alkaline formaldehyde, the cell reached equilibrium after about 2 hr, but the potential still continued to vary slightly. This was in marked contrast to a solution of pure alkali in which the cell reached equilibrium in about an hour. Almost invariably the two hydrogen electrodes gave identical values in alkali and different values in alkaline formaldehyde when compared one with the other.

The relation between the results of previous workers and the present determination can be seen if the logarithm of the dissociation constant, $\log K_1$, is plotted against the reciprocal of the absolute temperature, $1/T$ (Fig. 1). There is an approximate linear relationship between $\log K_1$ and $1/T$ for all determinations.

Experimental

A carbonate-free 0·5N sodium hydroxide solution was prepared from a filtered 50 per cent. NaOH solution and stored in a " Polythene " bottle. Its concentration was determined by titration with standard acid.

A formaldehyde solution, prepared by refluxing paraformaldehyde with water, was distilled under vacuum from a slightly alkaline solution to remove

traces of formic acid. The distillate was filtered from the polymer which separates, analysed by Romijn's cyanide method (Walker 1953, p. 388) and diluted to 0·5M. A CO_2-free atmosphere was maintained above the stock solutions by connecting the bottles through a soda lime tower to a cylinder of argon.

The test solution was prepared from aliquots of the stock solutions in a standard flask and was placed in the apparatus shown in Figure 2. The junction between the two electrodes was made by means of a B10 cone and socket and a tightly packed plug of filter paper. The two hydrogen electrodes were freshly prepared for each determination by the method of Hamer and Acree (1939), dried under a vacuum, and half-immersed in the test solution. The calomel electrode was prepared according to the method of Hills and Ives (1951).

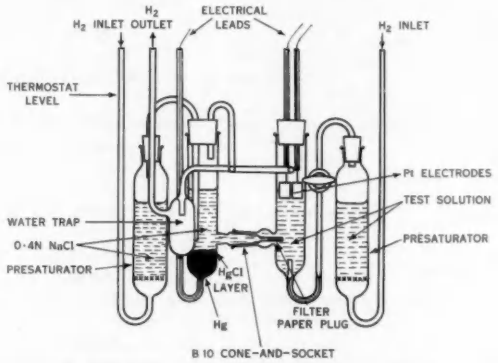


Fig. 2.—Diagram of apparatus for the cell
Hg | HgCl(s) | NaCl | NaOH, CH_2O, NaCl | H_2(g) | Pt black.

The solutions for both electrodes were 0·4N with respect to NaCl in order to reduce the junction potential to a minimum and maintain an ionic strength of $\mu = 0{\cdot}4$. When the calomel electrode was not in use, the filter paper junction was immersed in 0·4N NaCl in such a way that the solution tended to flow from the electrode. The potential of the calomel electrode varied and the cause was thought to be the junction potential.

Since the junction potential varied greatly with the hydroxyl ion concentration, it was necessary to standardize the calomel electrode frequently with standard NaOH solutions of an hydroxyl ion concentration approximating that of the CH_2O–NaOH system. The hydroxyl ion concentration CH_2O–NaOH system was then obtained by a linear interpolation or extrapolation. The potential of the cell for each particular concentration was measured several times with fresh solutions and the mean taken.

Since the hydroxyl ion concentration was measured directly, the hydrolysis constant was calculated and then converted to the dissociation constant with the usual relationship $K_h = K_w/K_1$, where K_w is $2{\cdot}71 \times 10^{-14}$ g-mol l^{-1} at 40 °C (Harned and Hamer 1933).

Both solutions in the cell were deaerated with hydrogen presaturated with water vapour by bubbling through solutions of the same composition. The whole cell including presaturators was immersed in an oil thermostat at 40 °C and the potential measured every 15 min with a Tinsley precision potentiometer until equilibrium had been established. To prevent dilution of the test solution the effluent hydrogen was passed through a trap. The potential of the cell was corrected for the hydrogen pressure as described by Hamer and Acree (1939).

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